CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215341Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Administrative Application Information

Category	Application Information
Application type	NDA
Application number(s)	215341
Priority or standard	Priority
Submit date(s)	11/6/2020
Received date(s)	11/9/2020
PDUFA goal date	7/9/2021
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	See electronic signature date
Established/proper name	Finerenone (BAY 94-8862)
(Proposed) proprietary name	KERENDIA
Pharmacologic class	Non-steroidal mineralocorticoid receptor antagonist
Code name	771000119108
Applicant	Bayer Healthcare Pharmaceuticals
Dosage form(s)/formulation(s)	Film-coated tablet
Dosing regimen	10 mg or 20 mg once daily
Applicant proposed indication(s)/ population(s)	To (b) (4) reduce the risk of (b) (4) cardiovascular (b) (4) death, non-fatal myocardial infarction, (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2D)
Proposed SNOMED indication	Chronic kidney disease due to type 2 diabetes mellitus
Regulatory action	Approval
Approved dosage (if applicable)	Recommended starting dose of 10 mg once daily in patients with an eGFR of 25 to <60 mL/min/1.73 m^2 and 20 mg once daily in patients with an eGFR ≥60 mL/min/1.73 m^2; target daily dose of 20 mg
Approved indication(s)/ population(s) (if applicable)	To reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease associated with type 2 diabetes
Approved SNOMED term for indication (if applicable)	Chronic kidney disease due to type 2 diabetes mellitus

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Glossary

ACE	angiotensin converting enzyme
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AKI	acute kidney injury
ARB	angiotensin receptor blocker
AUC	area under the concentration-time curve
BEI	biliary excretion index
BID	twice daily
BMI	body mass index
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
C_{max}	maximum plasma concentration
CYP	Cytochrome P450
DKD	diabetic kidney disease
DMC	data monitoring committee
EC_{50}	half maximal effective concentration
ECAC	executive carcinogenicity assessment committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOS	end of study
EPC	established pharmacologic class
ESKD	end stage kidney disease
FAS	full analysis set
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities Query
GCP	good clinical practice
GLP	good laboratory practice
hERG	human ether-a-go-go-related gene
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICH	International Conference on Harmonisation
IND	investigational new drug
IRD	incidence risk difference
ITT	intent-to-treat
IV	intravenous
LD	lactation day
LS-mean	least squares mean
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
MR	mineralocorticoid receptor

MRA	mineralocorticoid receptor antagonist
MRHD	maximum recommended human dosage
NDA	new drug application
NOAEL	no observed adverse effect level
OCP	Office of Clinical Pharmacology
PD	pharmacodynamic
PEG	polyethylene glycol
PK	pharmacokinetic
PT	preferred term
QD	once daily
RIS	relative induction score
RRT	renal replacement therapy
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	standard of care
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TK	toxicokinetic
UACR	urine albumin-to-creatinine ratio

I. Executive Summary

1. Summary of Regulatory Action

On November 6, 2020, Bayer Healthcare Pharmaceuticals submitted a New Drug Application for finerenone (b) (4) to reduce the risk of (b) (4) cardiovascular (CV) (b) (4) death, non-fatal myocardial infarction, (b) (4) and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes (T2DM). Finerenone is a non-steroidal, selective mineralocorticoid receptor antagonist. Mineralocorticoid receptors are expressed in the kidneys, heart, and blood vessels, and overactivation is thought to contribute to fibrosis and inflammation.

Overview of disease and available therapies
Diabetes is the most common cause of CKD and kidney failure in the United States. Available therapies for diabetic kidney disease include angiotensin receptor blockers, angiotensin converting enzyme inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors. Other interventions believed to delay the progression of diabetic kidney disease include blood pressure and glucose control. Despite such interventions, many patients experience a progressive loss of kidney function.

Efficacy Findings

In support of the proposed indication, the Applicant submitted the results of a randomized, double-blind, placebo-controlled, international study in 5,674 adult patients with type 2 diabetes mellitus and a clinical diagnosis of diabetic kidney disease receiving standard of care, as defined at the start of the trial, including a maximum tolerated labeled dose of an angiotensin converting enzyme inhibitor or angiotensin receptor blocker. [1] The trial met its primary endpoint, a composite endpoint that included a sustained decline in eGFR of ≥40%, kidney failure, or renal death (HR 0.82, 95% CI: 0.73-0.93, p=0.001). The treatment effect reflected a reduction in a sustained decline in eGFR of ≥40% and progression to kidney failure. Finerenone also significantly reduced the risk of the key composite secondary endpoint of time to the first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HR 0.86, 95% CI: 0.75-0.99, p=0.03). The treatment effect on this composite endpoint reflected a reduction in CV death, non-fatal myocardial infarction, and hospitalization

[1] Since the initiation of the phase 3 trial, there have been advances in the treatment of patients with CKD associated with T2DM. In 2019, the sodium-glucose co-transporter 2 (SGLT2) inhibitor canagliflozin was approved to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria. In 2021, the SGLT2 inhibitor dapagliflozin was approved to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with CKD at risk of progression (a broader population that includes patients with CKD associated with T2DM).

for heart failure. The treatment effect on the primary and secondary composite endpoints was generally consistent across subgroups.[2]

Safety
Risks of finerenone as observed in the phase 3 trial were generally consistent with its mechanism of action. The most frequently reported adverse reaction was hyperkalemia, which was reported in 18% of patients randomized to finerenone as compared to 9% of patients randomized to placebo. Hyperkalemia led to permanent discontinuation of treatment in 2.3% of patients receiving finerenone as compared to 0.9% of patients receiving placebo and resulted in hospitalization in 1.4% of patients receiving finerenone as compared to 0.3% receiving placebo.

Safety analyses also focused on other potential risks related to the product's mechanism of action as well as the experience with approved mineralocorticoid receptor antagonists. With regard to these risks:

- Adverse events of hypotension, dehydration and hyponatremia were reported at a slightly greater incidence in the finerenone as compared to placebo arm (4.8% finerenone versus 3.4% placebo for hypotension, 1.7% finerenone versus 1.2% placebo for dehydration, and 1.4% finerenone versus 0.7% placebo for hyponatremia).
- Adverse events of gynecomastia were uncommon and were reported at a similar incidence in the two treatment arms (0.2% finerenone versus 0.4% placebo).

Conclusion
The review team believes that the submitted data provide substantial evidence of finerenone's effectiveness in reducing the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, myocardial infarction, and hospitalization for heart failure in adults with type 2 diabetes mellitus (b) (4), and believe that the clinical benefits clearly outweigh the risks. Given the safety findings in the development program, labeling will include a Warning and Precaution for hyperkalemia and instructions on how to monitor for and mitigate this risk.

[2] Because SGLT2 inhibitors were only recently approved for renal-related indications, only 4.6% of patients were taking SGLT2 inhibitors at baseline in finerenone's phase 3 trial; given the limited size of the population on SGLT2 inhibitors at baseline, it is difficult to draw meaningful conclusions from subgroup analyses in this population.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Diabetes affects an estimated 23 million adults in the United States with over 1.4 million new cases diagnosed annually. Approximately 95% of these individuals have type 2 diabetes mellitus (T2DM). • Approximately 30 to 40% of patients with diabetes will develop chronic kidney disease related to their diabetes. Approximately 20% of these patients will progress to end stage kidney disease (ESKD) over 20 years. Diabetes is the most common cause of ESKD in the United States. • Patients with T2DM and diabetic kidney disease are at high risk for cardiovascular (CV) events, including myocardial infarction, stroke, heart failure, and death.	Chronic kidney disease associated with T2DM is common in the United States and is associated with significant morbidity and mortality.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The angiotensin receptor blockers irbesartan and losartan are approved for the treatment of diabetic nephropathy in T2DM. Captopril, an angiotensin converting enzyme inhibitor, is approved for the treatment of diabetic nephropathy in type 1 diabetes. The beneficial effects of these agents on the kidney are generally considered to reflect a "class effect" that applies to both angiotensin converting enzyme inhibitors and angiotensin receptor blockers. As such, these agents are considered standard of care for the treatment of CKD associated with T2DM. • There have been recent advances in the treatment of patients with CKD associated with T2DM. In 2019, the sodium-glucose co-transporter 2 (SGLT2) inhibitor canagliflozin was approved to reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and hospitalization for heart failure in adults with T2DM and diabetic nephropathy with albuminuria. In 2021, the SGLT2 inhibitor dapagliflozin was approved to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with CKD at risk of progression (a broader population of patients that includes patients with CKD associated with T2DM). • Other interventions believed to delay the progression of diabetic kidney disease include blood pressure and glucose control.	While there have been recent important advances in the treatment of patients with CKD associated with T2DM, there is still significant unmet medical need for treatments that reduce morbidity and mortality in this population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• In FIDELIO-DKD, a randomized, double-blind, placebo-controlled, multicenter study in 5674 adult patients with T2DM and a clinical diagnosis of diabetic kidney disease, finerenone reduced the incidence of the primary composite endpoint of a sustained decline in eGFR of ≥40%, kidney failure, or renal death (HR 0.82, 95% CI: 0.73-0.93, p=0.001). The treatment effect reflected a reduction in a sustained decline in eGFR of ≥40% and progression to kidney failure. There were few renal deaths during the trial. • Finerenone also significantly reduced the risk of the key composite secondary endpoint of time to the first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure (HR 0.86, 95% CI: 0.75-0.99, p=0.03).The treatment effect on this composite endpoint reflected a reduction in CV death, non-fatal MI, and hospitalization for heart failure.	The submitted data provide substantial evidence of finerenone's effectiveness in reducing the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, myocardial infarction, and hospitalization for heart failure in adults with type 2 diabetes mellitus (b) (4) (b) (4).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In FIDELIO-DKD, 2827 patients received at least one dose of finerenone and 2831 patients received at least one dose of placebo. Serious adverse events occurred in 32% of patients receiving finerenone and in 34% of patients receiving placebo. Approximately 7% of patients in the finerenone arm and 6% of patients in the placebo arm discontinued study drug because of an adverse event. • Risks of finerenone as observed in FIDELIO-DKD were generally consistent with its mechanism of action. The most frequently reported adverse event was hyperkalemia, which was reported in 18% of patients randomized to finerenone as compared to 9% of patients randomized to placebo. Hyperkalemia led to permanent discontinuation of treatment in 2.3% of patients receiving finerenone as compared to 0.9% of patients receiving placebo and resulted in hospitalization in 1.4% of patients receiving finerenone as compared to 0.3% receiving placebo. • Adverse events of hypotension, dehydration and hyponatremia were reported at a slightly greater incidence in the finerenone as compared to placebo arm (4.8% finerenone versus 3.4% placebo for hypotension, 1.7% finerenone versus 1.2% placebo for dehydration and 1.4% finerenone versus 0.7% placebo for hyponatremia). Adverse events of gynecomastia were uncommon and were reported at a similar incidence in the two treatment arms (0.2% finerenone versus 0.4% placebo).	Risks of finerenone as observed in the FIDELIO-DKD trial were, for the most part, consistent with its mechanism of action (i.e., selective mineralocorticoid receptor antagonist). Hyperkalemia was the most common adverse reaction. Labeling is considered sufficient to ensure that the benefits of finerenone in the target population outweigh its risks.

2.2. Conclusions Regarding Benefit-Risk

The submitted data provide substantial evidence of finerenone's effectiveness in reducing the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, myocardial infarction, and hospitalization for heart failure in adults with type 2 diabetes mellitus (b) (4); these clinical benefits clearly outweigh the product's risk. Hence, the review team recommends approval of finerenone.

II. Interdisciplinary Assessment

3. Introduction

The Applicant has submitted a new drug application (NDA) for KERENDIA (finerenone) "to [redacted] reduce the risk of [redacted] cardiovascular death, non-fatal myocardial infarction, [redacted] hospitalization for heart failure in adult patients with chronic kidney disease (CKD) and type 2 diabetes."

Diabetes affects an estimated 23 million adults in the United States with over 1.4 million new cases diagnosed annually. Approximately 95% of these individuals have type 2 diabetes mellitus (T2DM). Despite current therapies, the morbidity and mortality of diabetes remain high. Approximately 30 to 40% of patients with diabetes will develop CKD related to their diabetes. T2DM is the most common cause of ESKD in the United States and worldwide. In most patients, the diagnosis of diabetic kidney disease (DKD)[3] is a clinical diagnosis (i.e., the diagnosis is based on clinical history and laboratory evaluation as opposed to a kidney biopsy). The most common clinical abnormalities in patients with DKD are persistent albuminuria and/or a sustained decrease in estimated glomerular filtration rate (eGFR). Patients with DKD are also at high risk for cardiovascular events, including myocardial infarction, stroke, and heart failure.

The renin-angiotensin system inhibitors captopril, irbesartan, and losartan were approved over 15 years ago for the treatment of diabetic nephropathy in patients with either type 1 diabetes mellitus (T1DM) or T2DM (Table 3), although the beneficial effects are generally considered to be a class effect that applies to other angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). In 2019, the sodium-glucose co-transporter 2 (SGLT2) inhibitor canagliflozin was approved to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria. In 2021, the SGLT2 inhibitor dapagliflozin was approved to reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with CKD at risk of progression (a broader population of patients that includes patients with CKD associated with T2DM). Other interventions believed to delay the progression of DKD include blood pressure and glucose control. Despite these interventions, many patients experience progressive disease. Hence, there remains an unmet medical need for additional treatments for patients with DKD.

[3] This review uses the terms "diabetic kidney disease (DKD)," "diabetic nephropathy," "CKD associated with T2DM," and "clinical diagnosis of DKD" interchangeably to refer to patients with clinically-diagnosed CKD thought to be caused by T2DM.

Table 3. Drugs Approved for the Treatment of Diabetic Nephropathy

Drug	Indication
Angiotensin Converting Enzyme Inhibitors	
Captopril	For the treatment of diabetic nephropathy (proteinuria >500 mg/day) in patients with type I insulin-dependent diabetes mellitus and retinopathy. Captopril tablets decrease the rate of progression of renal insufficiency and development of serious adverse clinical outcomes (death or need for renal transplantation or dialysis)
Angiotensin Receptor Blockers	
Irbesartan	For the treatment of diabetic nephropathy in patients with type 2 diabetes and hypertension, an elevated serum creatinine, and proteinuria (>300 mg/day). In this population, irbesartan tablets reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end-stage renal disease (need for dialysis or renal transplantation)
Losartan	For the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria (urinary albumin to creatinine ratio ≥300 mg/g) in patients with type 2 diabetes and a history of hypertension. In this population, Losartan potassium tablet reduces the rate of progression of nephropathy as measured by the occurrence of doubling of serum creatinine or end stage renal disease (need for dialysis or renal transplantation)
Sodium-Glucose Co-Transporter 2 Inhibitors	
Canagliflozin	To reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria
Dapagliflozin	To reduce the risk of sustained eGFR decline, end-stage kidney disease, CV death, and hospitalization for heart failure in adults with CKD at risk of progression (a broader population of patients that includes patients with CKD associated with T2DM)

Source: Captopril, irbesartan, losartan, canagliflozin and dapagliflozin labels

Finerenone is a non-steroidal, selective mineralocorticoid receptor antagonist (MRA). Mineralocorticoid receptors are expressed in the kidneys, heart, and blood vessels, and overactivation is associated with inflammation and fibrosis; antagonism of the receptor has been associated with attenuation of such effects. Compared to steroidal MRAs, finerenone does not interfere with the steroid hormone receptor, and is therefore not expected to cause sexual side effects, such as gynecomastia, in men.

In support of the proposed indication, the Applicant conducted a single phase 3 trial (16244) titled, "A randomized, double-blind, placebo-controlled, parallel group, multicenter, event-driven Phase III study to investigate the efficacy and safety of finerenone, in addition to standard of care, on the progression of kidney disease in subjects with type 2 diabetes mellitus and the clinical diagnosis of diabetic kidney disease" (FIDELIO-DKD; Table 4).

The Applicant also has an on-going randomized, double-blind, placebo-controlled phase 3 trial (17530) (FIGARO-DKD) investigating the efficacy and safety of finerenone in addition to standard of care on the reduction of cardiovascular morbidity and mortality in patients with T2DM and earlier stages of chronic kidney disease, with expected completion in 2021.

3.1. Review Issue List

3.1.1. Key Review Issues Relevant to Evaluation of Benefit

No finding rose to the level of a "key review issue."

3.1.2. Key Review Issues Relevant to Evaluation of Risk

No finding rose to the level of a "key review issue."

3.2. Approach to the Review

This was a joint review. Dali Zhou focused on the data supporting efficacy. Rekha Kambhampati focused on the data supporting safety.

Table 4. Clinical Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Finerenone

Trial Identifier (NCT#)	Trial Population	Trial Design	Dosing Regimen	Primary and Key Secondary Endpoint	Number of Subjects Randomized	Number of Centers and Countries
16244	FIDELIO-DKD	Phase 3, multicenter, randomized, placebo-controlled, double-blind	Starting dose: either 10 mg OD for eGFR 25 to <60 mL/min/1.73 m^2 or 20 mg OD for eGFR ≥60 mL/min/1.73 m^2 in addition to standard of care with stable ACEi or ARB Up-titration to maximum of 20 mg OD allowed for lower starting dose	Primary: Time to first occurrence of the composite endpoint of onset of kidney failure, sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death Key Secondary: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure	N 5674	1024 centers in 48 countries

Source: Reviewer
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: BID, twice daily; N, number of subjects; CV, cardiovascular; MI, myocardial infarction; eGFR, estimated glomerular filtration rate; OD, once daily; mg, milligram; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

4. Patient Experience Data

No patient experience data were collected during the FIDELIO-DKD trial.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical outcome assessment data submitted in the application		
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other patient experience data submitted in the application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

Table 6. Summary of General Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Non-steroidal mineralocorticoid receptor antagonist
Mechanism of action	Finerenone is a potent and selective nonsteroidal antagonist of the mineralocorticoid receptor that reduces inflammation and fibrosis due to overactivation of the mineralocorticoid receptor.
Active moieties	Finerenone
QT prolongation	Safety pharmacology in beagle dogs with doses of finerenone ranging from 0 to 10 mg/kg showed QTc intervals were unaffected after finerenone administration. In humans given a single dose of 20 mg or 80 mg of finerenone, the upper limits of the one-sided 95% CIs of the mean differences to placebo of QTcF values were below the 10 msec threshold, indicating no clinically relevant effect after administration.
	General Information
Bioanalysis	Validated LC-MS/MS methods were used to determine the concentrations of finerenone and its metabolites in human plasma and urine (as applicable to individual studies).
Healthy subjects versus patients	PK is different in the patient population, primarily owing to impairment of renal function, compared to a healthy population. Exposures (AUC) are between 15% lower and 36% higher in patients with renal impairment as compared to healthy volunteers, depending on their renal function status (see Renal Impairment section for details).
Drug exposure at steady state following the therapeutic dosing regimen (or single dosage, if more relevant for the drug)	**Parameter** / **Geometric Mean ± SD** / **Dose** $C_{max,md}$ / 80 µg/L +1.3 / 10 mg $AUC_{T,md}$ / 343 µg·h/L +1.3 / 10 mg $C_{max,md}$ / 160 µg/L +1.3 / 20 mg $AUC_{T,md}$ / 686 µg·h/L +1.3 / 20 mg Source: Applicant's popPK analysis of the FIDELIO-DKD study
Range of effective dosage(s) or exposure	In the ARTS-DN Study (Study 16243), placebo-corrected UACR reductions were 21, 25, 33, and 35% for those treated with finerenone once daily at 7.5, 10, 15, and 20 mg, respectively. The 10 and 20 mg tablets are the proposed strengths for the commercial products, with 10 mg available as an initiation dose for those with an eGFR of 25 to <60 mL/min/1.73 m^2, and 20 mg as the target dose. According to dose-exposure-response modeling and simulation, finerenone effects are saturated at the 20 mg dose.
Maximally tolerated dosage or exposure	This was not explicitly tested, though the highest tested dose was a single dose administration of 80 mg in the form of 8 x 10 mg tablets in the fasted state (Study 13784). The highest multiple dose administration was 40 mg once daily (Study 13785). There were no obvious dose limiting toxicities in these studies in healthy volunteers.
Dosage proportionality	Dose proportionality has been demonstrated over a range of 1.25 and 80 mg (Study 15528).

Characteristic	Drug Information
Accumulation	Accumulation ratio AUC: 1.21 for 10 mg BID, 1.33 for 20 mg BID, 1.11 for 40 mg once daily Accumulation ratio: C_{max}:1.19 for 10 mg BID, 1.0 for 20 mg BID, 0.9 for 40 mg once daily Although not directly tested, accumulation is expected to be limited at the clinical doses of 10 mg QD and 20 mg QD. Source: Study 13785 – healthy volunteers
Time to achieve steady-state	Steady-state PK was achieved after 2 days.
Bridge between to-be-marketed and clinical trial formulations	The Applicant stated the Phase IIb-III formulation and the proposed commercial products are very similar, with differences (b) (4). Core composition (b) (4) - (b) (4) are the same in the Phase IIb-III tablets and the proposed commercial tablets. No bioequivalence study was conducted or requested because the formulation differences were so minor that they would not be expected to impact bioavailability.
Absorption	
Bioavailability	Absolute bioavailability is 43.5%.
T_{max}	The median T_{max} was 0.75 h when administered as a single 10-mg tablet, and 0.5 h when a 20-mg dose was administered as 2 x 10-mg tablets.
Food effect (fed/fasted) Geometric least square mean and 90% CI	10-mg tablet of finerenone taken with a high-fat, high calorie breakfast: (Study 13784) $AUC_{0-\infty}$: 110.0 (102.1 – 118.6) C_{max}: 67.7 (59.4 – 77.2) T_{max} (median): fasted – 0.75 h; fed – 2.5 h Study completed with the Phase I/IIa tablet 20-mg tablet of finerenone taken with a high-fat, high calorie breakfast: (Study 16536) $AUC_{0-\infty}$: 120.9 (112.5 – 129.9) C_{max}: 81.3 (70.1 – 94.2) T_{max} (median): fasted – 0.75 h; fed – 2.5 h Study completed with the Phase IIb/III tablet which is similar to the to-be-marketed product
Distribution	
Volume of distribution	V_{ss}: 52.6 L in Study 16535 (1 mg IV) Vz/F: 140 L in Study 14509 (10-mg tablet; normal renal function)
Plasma protein binding	Finerenone is mainly bound to albumin in human plasma, with some binding to α1-acidic glycoprotein, α-globulins, LDL and γ-globulins. Protein binding of finerenone in human plasma is 91.7%.
Drug as substrate of transporters	In vitro, finerenone is a substrate of P-gp. When tested in the mass-balance study, complete absorption was observed after oral administration, indicating that P-gp mediated transport is of little significance clinically. Other in vitro drug transporter studies reviewed showed that finerenone was not a substrate for OATP1B1, OATP1B3, OCT1, or BCRP. More detailed information on the substrate activity of finerenone and its metabolites is presented in Section III.14.1.

Characteristic	Drug Information
	Elimination
Mass balance results	Following administration of 10 mg of $^{[14C]}$finerenone in an aqueous solution, 79.6% of the dose was recovered in urine and 21.2% was recovered in feces. Unchanged finerenone represented about 0.184% of the administered dose in feces and 0.825% in urine (KINM-110111-ELB, Report PH-39577). The four major metabolites were pharmacologically inactive and were M1a and M1b (from oxidation of the dihydropyridine moiety to a pyridine), M2a (resulting from subsequent hydroxylation of a methyl group), and M3a (further oxidation leading to a carboxylic acid).
Clearance	For a 1-mg dose administered IV, the plasma CL is 22.3 L/h. CL/F for 10 mg $^{[14C]}$finerenone aqueous solution is 48.7 L/h. Following administration of a 10-mg tablet, CL/F is 43.0 L/h, 50.4 L/h, 28.4 L/h, 32.2 L/h, and 31.6 L/h for those with CL_{CR} $\geq$90 mL/min, CL_{CR} 60 to <90 mL/min, CL_{CR} 30 to <60 mL/min, and CL_{CR} 15 to <30 mL/min, respectively.
Half-life	$T_{1/2}$ at steady state in the FIDELIO study was ~ 2.6 hours.
Metabolic pathway(s)	In vitro studies demonstrated that both CYP3A4 and CYP2C8 contribute to the metabolism of finerenone. CYP3A4 was found to be primarily responsible for metabolism, accounting for 87-89% of the metabolic clearance for finerenone. CYP2C8 was largely responsible for the rest of the metabolic clearance. In vivo studies showed that CYP3A4 was largely responsible for finerenone metabolism, as concomitant administration with CYP3A4 inhibitors greatly increased finerenone AUC and C_{max}; however in vivo studies showed that CYP2C8 did not contribute as much to finerenone metabolism, as concomitant administration with a strong CYP2C8 inhibitor, gemfibrozil, increased finerenone AUC and C_{max} by only 10.1% and 15.7%, respectively.
	Intrinsic Factors and Specific Populations
Body weight	No study in the clinical pharmacology program specifically assessed the influence of body weight on exposure. However, body weight was identified as a statistically significant covariate on finerenone's volume of distribution and clearance and had a clinically meaningful impact on finerenone's C_{max}. Based on population PK analyses, patients with body weights greater than the 95th percentile (121 Kg) are estimated to have at least 20% lower C_{max} compared to a typical patient with a body weight of 85 Kg.
Age	A single-dose age and gender study was conducted. When comparing those > 65 years old to those < 45 years old, there was an increase in mean AUC and C_{max} by 34% and 51%, respectively. When normalized for body weight, these differences were smaller, with AUC_{norm} 27% higher in elderly and $C_{max,norm}$ 43% higher in the elderly. In a popPK analysis of the FIDELIO-DKD study, the geometric means for $C_{max,md}$ and $AUC_{\tau,md}$ (for both the 10 mg and 20-mg doses) were similar for those <65 and those $\geq$65 years.
Renal impairment	As compared to patients with an eGFR $\geq$90 mL/min/1.73 m^2, the LS-mean %-ratios for C_{max} values in patients with an eGFR of 60 to <90 mL/min/1.73 m^2, eGFR 30 to <60 mL/min/1.73 m^2, and eGFR 15 to <30 mL/min/1.73 m^2 were 78%, 88%, and 74%, respectively, after a single 10-mg dose (excluding 1 outlier). As compared to those with an eGFR $\geq$90 mL/min/1.73 m^2, the LS-mean %-ratios for AUC values for patients with an eGFR 60 to <90 mL/min/1.73 m^2, eGFR 30 to <60 mL/min/1.73 m^2, and eGFR 15 to <30 mL/min/1.73 m^2 were 82%, 138%, and 117%, respectively, after a single 10-mg dose (excluding 1 outlier).
Hepatic impairment	The LS-mean %-ratios for C_{max} values in patients with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment as compared to healthy individuals were 96.4 and 99.1%, respectively, after a single 5-mg dose. The LS-mean %-ratios for AUC values for those with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment compared to healthy individuals were 108.4 and 138.3%, respectively, after a single 5-mg dose.

Characteristic	Drug Information				
	Drug Interaction Liability (Drug as Perpetrator)				
Inhibition/induction of metabolism	**Enzyme**	**IC_{50} (μM)**	**Model**	**$1+[I]K_i$**	**Threshold Cutoff for Potential DDI**
	CYP2C8	6.8	Basic (systemic) Mechanistic (systemic)	1.021 1.18	≥1.02 ≥1.25
	CYP1A1 (+ pre-incubation without NADPH)	9.5	Basic (tested CYP1A1) (systemic)	1.012	≥1.02
	CYP1A1 (+ pre-incubation + NADPH)	3.7			
	CYP3A4 testosterone 6β-hydroxylation tested with ketoconazole	19	Basic CYP3A4/midazolam, reversible (systemic)	1.005	≥1.02
	CYP3A4 testosterone 6β-hydroxylation tested with mibefradil	10	Basic CYP3A4/testosterone, reversible (systemic)	1.007	≥1.02
	CYP3A4 midazolam 1'-hydroxylation tested with ketoconazole	12	Basic CYP3A4 time-dependent inhibition (systemic)	9.29	$(k_{obs} + k_{deg})/ k_{deg} \geq 1.25$
	CYP3A4 [$^{13}C_6$]midazolam 1'-hydroxylation tested with mibefradil	6.4	Basic CYP3A4/midazolam (intestinal) Basic CYP3A4/testosterone (intestinal)	28.5 44.5	≥11 ≥11
	Additional information on other potential drug interactions that were evaluated in vitro is included in Section III.14.1. At the highest clinically relevant dose (20 mg QD), finerenone increased midazolam AUC by 11%. Repaglinide was administered alone, together with 20 mg of finerenone, or 3 hours after administration of 20 mg of finerenone to examine in vivo effects of finerenone on CYP2C8. The AUC of repaglinide increased by 12% when administered with finerenone and 10% when administered 3 hours after finerenone. Warfarin was administered after 20 mg finerenone had been administered once daily over 6 days. Finerenone had no clinically relevant effect on AUC or C_{max} of R- or S-warfarin.				
Inhibition/induction of transporter systems	**Transporter**	**IC_{50} (μM)**	**$[I]/IC_{50}$**	**Threshold Cutoff for Potential DDI**	
	BCRP	17	12.1	10	
	P-gp	47	4.5	10	
	These interactions are discussed in greater detail in Section III.14.1. In vivo, when 0.375 mg of digoxin was administered with 20 mg finerenone given once daily, digoxin PK was not significantly affected. No specific in vivo study was conducted to assess the effect of finerenone on BCRP. A dedicated in vivo study to assess the effect of finerenone on OATP1B1 and OATP1B3 transport proteins was not conducted; however, when finerenone was administered with repaglinide, the AUC of repaglinide increased by about 10%, likely reflecting a CYP2C8-related effect. These findings indicate that a clinically relevant DDI with OATP substrates is unlikely.				

Abbreviations: AUC, area under the curve; BID, twice daily; CL, clearance; CL_{CR}, clearance creatinine; DDI, drug-drug interaction; eGFR, estimated glomerular filtration rate; IC_{50}, half maximal inh bitory concentration; IV, intravenous; LC MS/MS, liquid chromatography with tandem mass spectrometry; LS-mean, least squares mean; PK, pharmacokinetics; PopPK, population pharmacokinetics; QD, once daily

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Primary Pharmacology of Finerenone (BAY 94-8862)

In vitro and in vivo studies indicate that BAY 94-8862 is a potent and selective mineralocorticoid receptor (MR) antagonist with protective effects on the heart and/or kidney in animal models of heart failure and chronic kidney disease. These effects were observed at dose levels that induced natriuresis in animals. Key findings are highlighted below:

- BAY 94-8862 was investigated in a panel of cell-based steroid hormone receptor transactivation assays. BAY 94-8862 had an IC50 of 17nM in a functional MR transactivation assay and did not exhibit any activity at other steroid hormone receptors at concentrations up to 10μM. Data obtained from radioactive binding assays confirmed that BAY 94-8862 is a selective and competitive MR antagonist at the full length MR. BAY 94-8862 blocks all relevant MR agonists (aldosterone and glucocorticoids) more potently than the steroidal MR antagonists spironolactone (by 2-fold on average) and eplerenone (by 40- to 70-fold). Lead profile screening (65 receptors, transporters and ion channels) conducted with BAY 94-8862 and its major human metabolites revealed no significant interactions (>50%) at 10 μM in any of the assays.
- BAY 94-8862 was evaluated in healthy animals as well as animal models of chronic heart failure and chronic kidney disease. BAY 94-8862 induced natriuresis in conscious rats at a dose of 0.3 mg/kg and was found to be 3- to 10-fold more potent in inducing natriuresis than eplerenone. In healthy conscious dogs, oral administration of doses of 10 mg/kg and greater resulted in a statistically significant increase in urinary Na+/K+ ratio. Aldosterone and potassium plasma levels were unaffected by short-term drug treatment.
- In a rat model of hypertension and heart failure induced by deoxycorticosterone acetate (a potent MR agonist), salt and unilateral nephrectomy, BAY 94-8862 showed pronounced end-organ protection effects, as demonstrated by a dose-dependent decrease in blood pressure, proteinuria, and heart and kidney weights after 10 weeks of treatment. Worsening of both the systolic (i.e., dp/dt) and diastolic (i.e., tau) functions was reduced, while cardiac hypertrophy was decreased in a dose-dependent manner. Renal function parameters, aldosterone-dependent proinflammatory and pro-fibrotic gene expression in the kidney all responded significantly at 1 mg/kg BAY 94-8862 in this model. Plasma proBNP was also dose-dependently decreased by BAY 94-8862, with a minimum effect dose of 1 mg/kg.
- In a rat chronic myocardial infarction model, BAY 94-8862 showed a pronounced protective effect against the development heart failure, as demonstrated by improvements in hemodynamic functions as well as plasma proBNP level at doses of 1 mg/kg. The activities of the steroidal MR antagonists spironolactone and eplerenone and the nonsteroidal MR antagonist BAY 94-8862 were compared in a chronic study in the stroke-prone spontaneous hypertensive rat model. BAY 94-8862 showed pronounced protection from morbidity and mortality in this animal model. Histopathological evaluation revealed clear myocardial and renal protection from degeneration and fibrosis. Renal function was also protected by

BAY 94-8862 in this model. In all parameters evaluated in this model, BAY 94-8862 (10 mg/kg) exhibited more significant end organ protective effects than spironolactone (30 mg/kg) or eplerenone (30 mg/kg).

Established Pharmacologic Class The following rationale supports the establishment of a new established pharmacologic class (EPC) (nonsteroidal mineralocorticoid receptor antagonist) for finerenone:

- Finerenone's nonsteroidal structure differs from the steroidal ring structure of approved mineralocorticoid receptor (MR) antagonists (i.e., spironolactone and eplerenone).
- The pharmacodynamic profile of finerenone and steroidal MR antagonists differs. Specifically, finerenone exhibits greater MR selectivity and higher MR affinity and appears to provide greater end organ protection in animal models of heart and kidney disease.
- The safety profile of finerenone differs from the safety profile of steroidal MR antagonists. In contrast to steroidal MR antagonists, finerenone does not appear to cause gynecomastia and may be associated with a lower rate of hyperkalemia.

6. Assessment of Effectiveness

6.1. Dose and Dose Responsiveness

Applicant's proposed dosing regimen

The proposed starting doses of finerenone are based on eGFR. Patients are to receive 20 mg once daily if their eGFR is ≥60 mL/min/m^2, and 10 mg once daily if their eGFR is ≥25 to <60 mL/min/1.73 m^2. The target daily dose of finerenone is 20 mg once daily. After 4 weeks, serum potassium and eGFR are used to determine finerenone doses. The Applicant's proposed eGFR- and potassium-based dosing strategy is shown in Table 7.

(b) (4)

Selection of dosing regimen for the phase 3 trial

Dose-exposure-response modeling and simulation indicate that effects of finerenone were largely saturated at 20 mg. In the ARTS-DN study, the treatment effect on UACR, a key PD endpoint, was approaching saturation at 20 mg of finerenone. At a 20 mg dose administered once daily,

there was a 38% decrease in UACR (placebo-corrected), with the greatest treatment effect observed at day 90.

The decision to select a once daily dosing regimen was supported by PK/PD modeling. Although the half-life of the drug is only 2 to 3 hours and the time to reach pharmacokinetic steady state is shorter, the time to onset of action appears to be longer than the pharmacokinetics of the drug, with model-predicted times to reach 99% steady-state drug effects on UACR, serum potassium, and eGFR at 138, 20, and 85 days, respectively. Half-lives for the effects on UACR, serum potassium, and GFR were about 18, 2, and 9 days, respectively, suggesting that dosing multiple times per day is not required.

Evaluation of the proposed dosing regimen

The Applicant is proposing a lower starting dose of 10 mg in patients with eGFR ≥25 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2 because finerenone increases serum potassium, and patients with lower levels of renal function are at greater risk of hyperkalemia as compared to patients with more preserved renal function. The dose of finerenone is then titrated up to 20 mg after 4 weeks, assuming eGFR has not decreased by more than 30% and the serum potassium is ≤4.8 mmol/L. This approach seems reasonable from a safety perspective.

Further support for the proposed dosing regimen of finerenone is provided by exposure-response analyses of data from the phase 3 study (FIDELIO-DKD). Predictions using the exposure-vs-serum potassium model indicate that, without dose modification and interruptions, serum potassium increases with increasing finerenone dose, implying a greater risk of hyperkalemia at doses higher than 20 mg (Figure 39). In contrast, analyses of exposure-vs-time to the renal composite outcome suggest that the 10 mg and 20 mg doses provide sufficient exposure for the intended treatment effect. Specifically, the concentration associated with half of the maximum drug effect (0.165 µg/L) is much lower than the average steady state-concentration at the 20 mg dose (32 µg/L). An exposure-vs-serum potassium model was also used to assess different serum potassium thresholds for initiation and titration of finerenone from 10 mg to 20 mg. Among the assessed thresholds, the initiation threshold of 5.0 mmol/L and titration threshold of 4.8 mmol/L were associated with the smallest relative risk of hyperkalemia (finerenone versus placebo).

6.2. Clinical Trial Intended to Demonstrate Efficacy

6.2.1. FIDELIO-DKD Trial

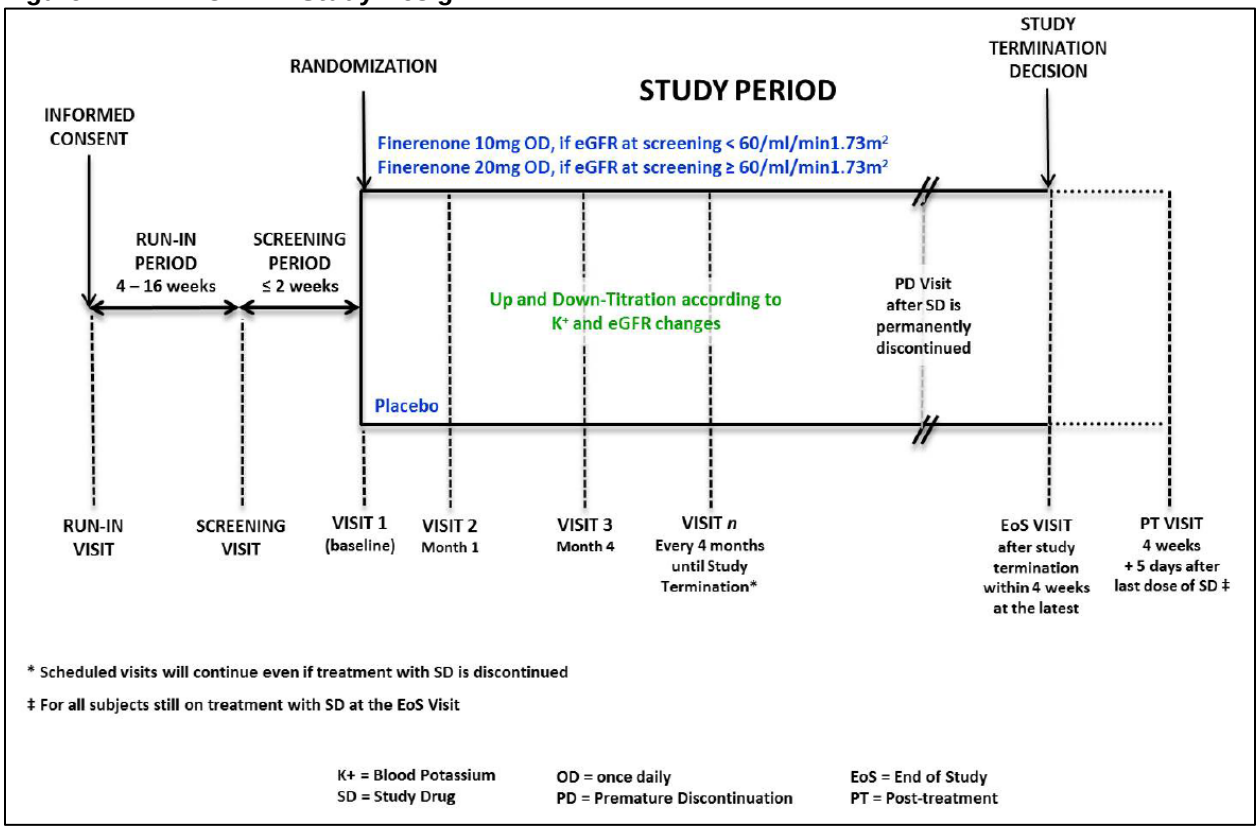
The protocol was issued on June 10, 2015 and was amended two times via global amendments (see Appendix Table 160 for details regarding each amendment). In the first global amendment (protocol Version 2.0 dated May 2, 2017), revisions were made to address a lower than expected recruitment rate. A total of 7264 patients were enrolled in the trial at that time. The second global amendment (protocol Version 3.0, dated February 26, 2019) contained minor revisions. The overview provided in this section is based on protocol Version 3.0.

6.2.1.1. Design

FIDELIO-DKD was a randomized, double-blind, parallel-group, event-driven trial comparing finerenone 10 mg or 20 mg once daily with placebo. The trial enrolled adults ≥18 years of age with type 2 diabetes mellitus and diagnosis of CKD who were receiving a maximum-tolerated daily dose of an ACE inhibitor or ARB. The diagnosis of CKD had to be accompanied by one of

the following criteria: (1) persistent "high" albuminuria (UACR ≥30 to <300 mg/g in 2 out of 3 first morning void samples) and eGFR ≥25 but <60 mL/min/1.73 m^2 (based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation) and presence of diabetic retinopathy or (2) persistent "very high" albuminuria (UACR ≥300 mg/g in 2 out of 3 first morning void samples) and eGFR ≥25 to <75 mL/min/1.73 m^2 (CKD-EPI equation). An overview of the study design is shown in Figure 1.

Figure 1. FIDELIO-DKD Study Design



Source: Applicant, FIDELIO-DKD Protocol

6.2.1.2. Objectives

The primary objective was to demonstrate whether, in addition to standard of care (SOC), finerenone was superior to placebo in delaying the progression of kidney disease, as measured by the composite endpoint of time to first occurrence of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death.

The secondary objectives of this study were to determine whether, in addition to SOC, finerenone compared to placebo:

- Delayed the time to first occurrence of the following composite endpoint: CV death or non-fatal CV events (i.e., non-fatal myocardial infarction, non-fatal stroke, hospitalization for heart failure)
- Delayed the time to all-cause mortality
- Delayed the time to all-cause hospitalization
- Resulted in a greater change in UACR from baseline to Month 4

- Delayed the time to first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death

6.2.1.3. Eligibility Criteria

Key inclusion criteria were as follows:

- Men or women aged 18 years or older
- Women of childbearing potential could only be included in the study if a pregnancy test was negative at the screening visit and if they agreed to use adequate contraception consisting of at least 2 effective methods of birth control, at least one of which was a physical barrier
- Type 2 diabetes mellitus as defined by the American Diabetes Association
- A clinical diagnosis of DKD based on either of the following criteria at the Run-in and Screening visits:

– Persistent "high" albuminuria defined as UACR of ≥30 mg/g and <300 mg/g in 2 out of 3 first morning void samples and eGFR ≥25 and <60 mL/min/1.73 m2 (CKD-EPI) and presence of diabetic retinopathy or
– Persistent "very high" albuminuria defined as UACR of ≥300 mg/g in 2 out of 3 first morning void samples and eGFR ≥25 and 75 mL/min/1.73 m^2 (CKD-EPI)

- Prior treatment with ACE inhibitors or ARBs, as follows:

– For at least 4 weeks prior to the Run-in visit, patient was treated with either an ACE inhibitor or ARB, or both
– Starting with the Run-in visit, patient was treated with only an ACE inhibitor or ARB
– For at least 4 weeks prior to the screening visit, patients were treated with the maximum tolerated labeled dose (but not below the minimum labeled dose) of only an ACE inhibitor or ARB (not both) preferably without any adjustments to dose or choice of agent.

- Serum potassium ≤4.8 mmol/L at both the Run-in and Screening visits

Key exclusion criteria were as follows:

- Known significant non-diabetic renal disease, including clinically relevant renal artery stenosis
- UACR >5000 mg/g at the run-in or screening visit
- HbA1c >12%
- Uncontrolled arterial hypertension with mean sitting SBP ≥170 mm Hg or mean sitting DBP ≥110 mm Hg at the Run-in Visit or mean sitting SBP ≥160 mm Hg or mean sitting DBP ≥100 mm Hg at the Screening Visit
- Mean SBP <90 mm Hg at the Run-in Visit or at the Screening Visit
- Subjects with a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II to IV) at the Run-in Visit

- Stroke, transient ischemic cerebral attack, acute coronary syndrome, or hospitalization for worsening heart failure, in the last 30 days prior to the Screening Visit
- Dialysis for acute renal failure within 12 weeks prior to the Run-in Visit
- Renal allograft in place or a scheduled kidney transplant within the next 12 months from the Run-in Visit
- Addison's disease
- Hepatic insufficiency classified as Child-Pugh C
- Concomitant therapy with eplerenone, spironolactone, any renin inhibitor, or potassium sparing- diuretic which could not be discontinued at least 4 weeks prior to the Screening visit
- Concomitant therapy with both ACEI and ARBs
- Concomitant therapy with potent CYP3A4 inhibitors or inducers (to be stopped at least 7 days before randomization)
- Pregnant or breast-feeding or intention to become pregnant during the study

6.2.1.4. Endpoints

Primary Endpoint

The primary endpoint was the time to the first occurrence of the composite endpoint of onset of kidney failure, a sustained decrease of eGFR ≥40% from baseline over at least 4 weeks, or renal death.

Kidney failure was defined as either the occurrence of ESRD or an eGFR of less than 15 mL/min/1.73 m^2, confirmed by a second measurement at least 4 weeks after the initial measurement. ESRD was defined as the initiation of chronic hemo- or peritoneal dialysis for at least 90 days or renal transplantation.

Renal death was defined by the presence of all 3 of the following criteria: (1) the patient died, (2) renal replacement therapy (RRT) had not been started in spite of being clinically indicated, and (3) there was no likely other cause of death.

Secondary Endpoint

The secondary endpoints were as follows:

- Time to first occurrence of the following composite endpoint: cardiovascular death or non-fatal cardiovascular events (i.e., non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure) ("key" secondary endpoint)
- Time to all-cause mortality
- Time to all-cause hospitalization
- Change in UACR from baseline to Month 4
- Time to the first occurrence of the following composite endpoint: onset of kidney failure, a sustained decrease of eGFR ≥57% from baseline over at least 4 weeks, or renal death

Cardiovascular death was defined as death resulting from acute myocardial infarction, sudden cardiac death, sudden death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, and death due to other cardiovascular causes.

Hospitalization due to heart failure was defined as an unplanned presentation to an acute care facility with a length of stay longer than 24 hours, with a primary diagnosis of heart failure.

See Section III.15 for details on the adjudication criteria for each of the definitions above.

6.2.1.5. Statistical Analysis Plan

The SAP was issued on August 3, 2016 and was amended three times. The final amendment (Version 4, dated February 14, 2020) was issued approximately 3 months before the end of study date (i.e., after the study was fully enrolled and 1078 (98%) of total confirmed primary endpoint events had accrued). Key revisions are summarized in Table 8. The study design, primary and secondary analyses, testing procedure, analysis sets definition, subgroup analysis strategy, and planned interim analysis were agreed upon at an End of Phase 2 meeting held in April 2015. The later revisions to the SAP did not change the agreed upon main analysis methods and strategies, and do not affect the interpretability of the efficacy results.

Table 8. Overview of SAP Amendments

SAP Version and Date	Amendment	Major changes
V2 dated 07 JUN 2019	From V1 to V2	Increased sample size by 1000 based on lower-than-expected event rate; Added exclusions to analysis sets of subjects with critical GCP violations; Added additional subgroup factors; Made modifications and additions to the sensitivity analyses for the primary and secondary efficacy variables.
V3 dated 12 SEP 2019	From V2 to V3	Provided full specification of testing procedure and multiplicity adjustment in a new SAP section; Provided specification of analysis for components of primary and secondary endpoints.
V4 dated 14 FEB 2020	From V3 to V4	Provided clarification on imputation rules for partially missing death dates; Added additional subgroups and reordered “key” and “important” subgroups.

Abbreviations: ACEIs/ARBs, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AE, adverse event; PPS, per protocol set; SAP, statistical analysis plan; UACR, urine albumin-to-creatinine ratio

Datasets

The SAP defined the following key datasets:

- *Safety Analysis Set:* All randomized subjects who took at least 1 dose of study drug (except those with critical GCP violations)
- *Full Analysis Set:* All randomized subjects (except those with critical GCP violations)
- *Per-Protocol Set:* All subjects in the full analysis set (FAS) who met a list of “validity” criteria.

Efficacy Analyses

Primary and secondary efficacy analyses for time to event variables were to be based on the FAS dataset. The data were to be analyzed using a stratified Cox proportional hazards model with randomization factors (region, type of albuminuria, and eGFR category) and a log rank test stratified by the randomization factors.

For the secondary endpoint change in UACR from baseline to Month 4, an analysis of covariance model was fitted to the logarithmized ratios of UACR at Month 4 to UACR at baseline, including the treatment group and stratification factors (region, type of albuminuria, and eGFR category) and the logarithmized baseline UACR as a covariate.

Stratification Factors

- Region (North America, Latin America, Europe, Asia, osthers)
- eGFR category at screening (eGFR 25 to <45, 45 to <60 and ≥60 mL/min/1.73m2)
- Type of albuminuria at screening (high albuminuria, very high albuminuria)

Interim Analysis

A formal interim analysis was planned at 2/3 of the required total number of primary efficacy endpoint events. The Haybittle-Peto rule was to be used to guide the decision regarding early stopping of the study for success: a value of 3 for the critical values with the standardized normal scale was to be used in the analysis of the primary and the key secondary efficacy endpoint at the interim analysis (two-sided p-value<0.0027).

Adjustment for Multiplicity

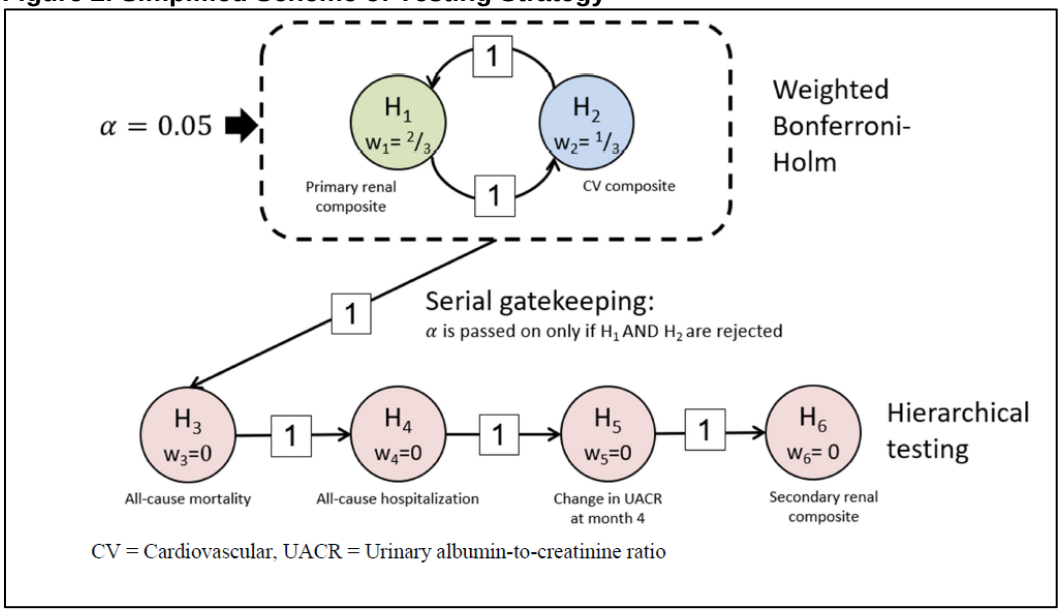
If the decision was made to stop early at the interim analysis for success, both the primary and secondary efficacy endpoints were to be tested at a two-sided significance level of 0.27%. If both primary and key secondary endpoint achieved this significance level, the remaining secondary endpoints were to be tested at a two-sided significance level of 0.27% according to the following hierarchy:

- Time to all-cause mortality
- Time to all-cause hospitalization
- Change in UACR from baseline to Month 4
- Time to first occurrence of the following renal composite endpoint: onset of kidney failure, a sustained decrease in eGFR of ≥57% from baseline over at least 4 weeks or renal death.

If the study was not stopped for success at the interim analysis, a combination of the weighted Bonferroni-Holm procedure and hierarchical testing was to be used (Figure 2), i.e., the 2-sided alpha used for the final analysis was to be adjusted to 0.0497 based on the group sequential design with a single interim analysis when 2/3 of the information was available with a stopping rule of a 2-sided p<0.0027. The testing procedure was specified as follows:

- If the primary renal composite endpoint achieves statistical significance at a two-sided p value ≤0.0328, the secondary CV endpoint will be tested at the 2-sided 0.0497 level.
- Alternatively, if the secondary CV endpoint achieves statistical significance at a 2-sided p value ≤0.0158, the primary renal composite endpoint will be tested at the two-sided 0.0497 level.
- Only if both the renal and CV endpoints achieve formal statistical significance, the remaining secondary endpoints will be tested at a two-sided level of 0.0497 according to the hierarchy above. This procedure controls the overall familywise error rate at 5% (Tang and Geller 1999).

Figure 2. Simplified Scheme of Testing Strategy



Source: Applicant's figure in CSR

Subgroup Analyses

Exploratory subgroup analyses were to be performed for the primary and key secondary efficacy variable. The subgroup analyses included the randomization stratification factors. In addition to the stratification factors, specified key subgroups included:

- History of cardiovascular disease (present, absent)
- Sex (male, female)
- Race (White, Black, Asian, other)
- Age at run-in visit (<65, ≥65 years)
- eGFR category at baseline (eGFR <25, 25 to <45, 45 to <60 and ≥60 mL/min/1.73m2)
- Type of albuminuria at baseline (normoalbuminuria (UACR <30 mg/g), high albuminuria, very high albuminuria)
- Baseline serum potassium value (≤ median and > median in the FAS)
- UACR at baseline (≤ median and > median in the FAS)
- Systolic blood pressure at baseline (≤ median and > median in the FAS)
- Baseline BMI (<30, ≥30 kg/m2)
- Hemoglobin A1C (≤7.5% />7.5%)
- SGLT-2 inhibitors treatment at baseline (yes, no)
- Glucagon-like peptide-1 agonists treatment at baseline (yes, no)

Censoring Rule

Events for inclusion in the primary analysis were to be counted from the day of randomization (planned at Visit 1) onwards until the end of study (EOS) visit following the study termination decision, or until the date of EOS notification +4 weeks if the EOS visit had not been performed.

In the event of premature discontinuation from the study with no subsequent follow-up information, renal events were to be counted up to the day of the last visit when complete information on all components of the composite renal endpoint was available.

For events occurring after the last eGFR visit in the period up to one day before the next planned clinic visit (maximum of 5 months: scheduled 4-month visit plus 1-month late attendance time window), additional rules applied:

- Kidney failure or renal death occurring in the above period after the last eGFR was recorded at a clinic visit were to be included in the efficacy analysis
- For non-renal deaths in this period, the date of death was to be used as the censoring date
- Randomized subjects without an event of the renal composite endpoint at the time of analysis were to be censored at the date of their last visit when complete information on all components of the composite renal endpoint was available, up to and including the EOS visit (should this visit satisfy this rule), or date of non-renal death using a time window of 5 months.
- Subjects without any information about the primary composite endpoint after baseline were to be censored at Day 1.

Missing Dates Imputation

A median imputation rule was to be used in case of availability of partial dates for clinical events in the efficacy analysis. A missing death was to be imputed on the basis of the last known contact when the subject was still alive and the first known contact when the subject was dead. In case both a non-fatal clinical event and death had partially missing dates, then the death date took precedence and was to be imputed first according to the rules above. This also applied for non-renal and non-CV deaths.

Sample Size Calculations

The trial was designed to achieve 90% power to demonstrate the superiority of finerenone to placebo using a log rank test. The projected sample size was 4800 randomized subjects (increased to 5800 in SAP version 2 to accommodate for a lower-than-expected event rate) to obtain at least 1068 primary efficacy endpoint events based on the following assumptions:

- Two-sided significance level 3.33%
- 20% relative risk reduction, i.e., a true hazard ratio of 0.80
- Study duration of 44 months
- Annual placebo event rate of 12%, a common annual lost to follow-up rate of 0.7% in both treatment groups, an annual finerenone discontinuation rate of 5% and the assumption that placebo discontinuations would not change the hazard.

6.2.1.6. Results of Analyses

Demographics and Baseline Clinical Characteristics

Baseline demographics were well-balanced between the two treatment arms (Table 9). The mean age was 66 years and 70% were male. The population was 63% White, 25% Asian and 5% Black or African American; 15% were of Hispanic or Latino ethnicity. Approximately 17% of trial participants were from North America and approximately 15% (824 patients) were from the U.S.

Table 9. Baseline Demographic, Full Analysis Set

Characteristic	Finerenone N=2833 (100%)	Placebo N=2841 (100%)
Sex, n (%)		
Male	1953 (68.9%)	2030 (71.5%)
Female	880 (31.1%)	811 (28.5%)
Age, years		
Mean (SD)	65.4 (8.9)	65.7 (9.2)
Median (min, max)	66 (32, 90)	66 (28, 97)
Age groups (years), n (%)		
18-44	49 (1.7%)	65 (2.3%)
45-64	1156 (40.8%)	1109 (39.0%)
65-74	1197 (42.3%)	1203 (42.3%)
≥75	431 (15.2%)	464 (16.3%)
Race, n (%)		
White	1777 (62.7%)	1815 (63.9%)
Black or African American	140 (4.9%)	124 (4.4%)
Asian	717 (25.3%)	723 (25.5%)
American Indian or Alaska Native	78 (2.8%)	76 (2.7%)
Native Hawaiian or other Pacific Islander	11 (0.4%)	7 (0.3%)
Not reported	9 (0.3%)	10 (0.4%)
Multiple	101 (3.6%)	86 (3.0%)
Ethnicity, n (%)		
Hispanic or Latino	447 (15.8%)	431 (15.2%)
Non-Hispanic or Latino	2376 (83.9%)	2397 (84.4%)
Not reported	10 (0.4%)	13 (0.5%)
Region, n (%)		
Europe	1182 (41.7%)	1176 (41.4%)
North America	467 (16.5%)	477 (16.8%)
Asia	790 (27.9%)	789 (27.8%)
Latin America	295 (10.4%)	298 (10.5%)
Others	99 (3.5%)	101 (3.6%)

Source: Applicant's table verified by statistical reviewer
Abbreviations: BMI, body mass index; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Baseline clinical characteristics were similar in the two treatment arms (Table 10). The mean eGFR was 44.3 mL/min/1.73 m^2, median UACR was 852 mg/g, mean HbA1C was 7.7% and mean BMI was 31 kg/m^2. Most (87.5%) of the patients had an albuminuria level of ≥300 mg/g. At baseline, 46% of patients had a history of CV disease. As previously noted, the trial excluded patients with a clinical diagnosis of chronic heart failure with reduced ejection fraction and persistent symptoms (New York Heart Association class II to IV) because MRAs carry a class 1 recommendation for use in this population.[4]

[4] Per the Applicant, other than the entry criteria provided to investigators, no specific directives were given to investigators regarding information that needed to be collected related to a patient's history of heart failure and ejection fraction (i.e., no systematic objective assessments such as ejection fraction were required to be collected or completed at baseline). Investigators were expected to assess and evaluate the medical history of the patient and any available supporting information to determine if the subject met the exclusion criteria for chronic heart failure with a reduced EF and persistent symptoms. The Applicant estimates that approximately 195 patients (6.9%) on finerenone and 241 (8.5%) on placebo, had "cardiac failure" at baseline; this estimate was derived by pooling the following preferred terms: acute left ventricular failure, cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac

As expected, given the protocol design, nearly all patients (99.9%) were on an ACE inhibitor or ARB at baseline. Approximately 97% of patients were on an antidiabetic agent, with the most common agent being insulin or an insulin-analogue (64%). Only 4.6% of patients were taking an SGLT2 inhibitor. As seen in the table below, 74% of patients were taking a statin and 57% were taking a platelet aggregate inhibitor at baseline.

Table 10. Baseline Clinical Characteristics, Full Analysis Set

Characteristic	Finerenone N=2833 (100%)	Placebo N=2841 (100%)
Baseline BMI (kg/m^2), n (%)		
Mean (SD)	31.13 (6.03)	31.10 (6.00)
Median (min, max)	30.4 (15.5, 63.7)	30.3 (14.5, 63.2)
Baseline BMI (kg/m^2) category, n (%)		
<20	22 (0.8%)	28 (1.0%)
≥20 - <25	348 (12.3%)	348 (12.2%)
≥25 - <30	950 (33.5%)	966 (34.0%)
≥30 - <35	866 (30.6%)	846 (29.8%)
≥35	635 (22.4%)	648 (22.8%)
Missing	12 (0.4%)	5 (2%)
Baseline eGFR (mL/min/1.73 m^2)		
Mean (SD)	44.36 (12.54)	44.32 (12.57)
Median (min, max)	43.00 (15.80, 107.20)	43.00 (15.80, 104.20)
Baseline eGFR (mL/min/1.73 m^2) category		
missing	1 (<0.1%)	1 (<0.1%)
<25	66 (2.3%)	69 (2.4%)
≥25 - <45	1476 (52.1%)	1505 (53.0%)
≥45 - <60	972 (34.3%)	928 (32.7%)
≥60	318 (11.2%)	338 (11.9%)
Baseline UACR (mg/g)		
Geom.Mean (Geom.SD)	798.79 (2.65)	814.73 (2.67)
Median (min, max)	832.72 (5.59, 7692.32)	867.01 (7.36, 8806.15)
Baseline UACR (mg/g) category		
≤851.9 (median in FAS)	1442 (50.9%)	1394 (49.1%)
>851.9 (median in FAS)	1389 (49.0%)	1446 (50.9%)
Missing	2 (<0.1%)	1 (0.1%)
Baseline albuminuria (mg/g) category		
<30	11 (0.4%)	12 (0.4%)
≥30 to <300	350 (12.4%)	335 (11.8%)
≥300	2470 (87.2%)	2493 (87.8%)
Missing	2 (<0.1%)	1 (0.1%)
Baseline Hemoglobin A1C (%)		
Mean (SD)	7.66 (1.33)	7.69 (1.36)
Median (min, max)	7.50 (4.30, 12.50)	7.50 (3.80, 12.90)

failure congestive, chronic left ventricular failure, left ventricular failure, oedema due to cardiac disease, right ventricular failure.

Characteristic	Finerenone N=2833 (100%)	Placebo N=2841 (100%)
History of CV disease, present		
Present	1303 (46.0%)	1302 (45.8%)
Absent	1530 (54.0%)	1539 (54.2%)
Duration of diabetes (years)		
Mean (SD)	16.58 (8.77)	16.55 (8.77)
Median (min, max)	16.12 (0.18, 53.15)	16.15 (0.17, 62.15)
Baseline medication use:		
ARB	1879 (66.3%)	1846 (65.0%)
ACEI	950 (33.5%)	992 (34.9%)
Statin	2105 (74.3%)	2110 (74.3%)
Insulins and analogues	1843 (65.1%)	1794 (63.1%)
GLP-1 agonists	189 (6.7%)	205 (7.2%)
SGLT-2 inhibitors	124 (4.4%)	135 (4.8%)
Biguanides	1251 (44.2%)	1239 (43.6%)
Platelet aggregate inhibitor[1]	1633 (57.6%)	1595 (56.1%)

Source: Applicant's table verified by statistical reviewer
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; FAS, full analysis set; max, maximum; min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation; UACR, urine albumin-to-creatinine ratio; ARB, angiotensin receptor blocker, ACEI, angiotensin converting enzyme inhibitor, GLP, glucagon-like peptide; SGLT, sodium-glucose co-transporter
[1]Excluding heparin

Disposition

A total of 13911 patients were screened for enrollment, of which 8177 were not eligible (screening failure). Those successfully screened were randomized to finerenone (N=2866) or placebo (N=2868). Of those who were randomized, 60 were excluded from the analyses because of GCP violations, all of which occurred at sites in the US. Thus, the FAS included 2833 patients randomized to finerenone and 2841 patients randomized to placebo (Table 11).

Table 11. Patient Randomization

Disposition	Finerenone	Placebo	Total
No. patients randomized	2866	2868	5734
GCP violations	33	27	60
Full analysis set	2833	2841	5674

Source: Applicant's table verified by statistical reviewer
Abbreviations: GCP, good clinical practice

Patients were considered to have completed the study if there was contact with the patient after the EOS notification or if the patient died. Based on this definition of study completion, 2824 patients in the finerenone arm and 2832 in the placebo arm completed the study. Vital status was unknown for 18 patients at the end of the study, 9 randomized to finerenone and 9 randomized to placebo (Table 12).

Table 12. Patient Disposition, Full Analysis Set

Disposition Category	Finerenone N=2833 n (%)	Placebo N=2841 n (%)
Completed study	2824 (99.7%)	2832 (99.7%)
Did not complete study	9 (0.3%)	9 (0.3%)
Lost to follow-up	5 (0.2%)	3 (0.1%)
Withdrawal consent	4 (0.1%)	6 (0.2%)

Source: Applicant's table verified by statistical reviewer
Abbreviations: N, number of patients; n, number of patients in specified population or group

Patients were considered to have "completed treatment" if they were not permanently discontinued from study drug at the time of the EOS notification (03 Feb 2020). Based on this definition, 1623 patients did not complete treatment: 822 (29%) in the finerenone arm and 801 (28%) in the placebo arm. The most frequently reported reasons for not completing treatment were "adverse or outcome event," withdrawal by patient, death, and physician decision (see Table 13).

Table 13. Treatment Completion, Full Analysis Set

	Finerenone N=2833 n (%)	Placebo N=2841 n (%)
Completed treatment	2011 (71.0%)	2040 (71.8%)
Did not complete treatment*	822 (29.0%)	801 (28.2%)
Adverse or outcome event	309 (10.9%)	294 (10.3%)
Withdrawal by subject	157 (5.5%)	169 (5.9%)
Death	130 (4.6%)	157 (5.5%)
Physician decision	148 (5.2%)	109 (3.8%)
Logistical difficulties	32 (1.1%)	32 (1.1%)
Non-compliance with study drug	18 (0.6%)	7 (0.2%)
Protocol deviation	7 (0.2%)	14 (0.5%)
Lost to follow-up	5 (0.2%)	4 (0.1%)

Source: Applicant's table verified by statistical reviewer
Abbreviations: N, number of subjects; n, number of subjects in specified population or group

Interim Analysis

A formal interim analysis was performed when 716 primary renal efficacy events (approximately 2/3 of the required total number of primary efficacy endpoint events) were identified (database cutoff date of July 8, 2019). The results of this analysis were reviewed by that Data Monitoring Committee (DMC) at a meeting on September 25, 2019.

The DMC observed that the analysis showed a favorable trend for the renal composite but not statistical significance and that the associated p-values were above 0.0027 (Table 14), the required level for the stopping rule for overwhelming efficacy. The observed hazard ratios for the primary renal and key secondary CV composite were also below the non-binding threshold of 0.977 for futility stopping; therefore, the DMC recommended that the study continue.

Table 14. Interim Analysis by DMC

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	HR	P-value
Primary renal Composite Endpoint	338 (11.9%)	378 (13.3%)	0.882	0.095
Secondary CV Composite Endpoint	266 (9.4%)	328 (11.5%)	0.804	0.008

Source: DMC meeting minutes
Abbreviations: CV, cardiovascular; DMC, data monitoring committee; HR, hazard ratio

Analysis of Primary Endpoint

The primary endpoint in the trial was the time to first occurrence of kidney failure (defined as eGFR <15 mL/min1.73m^2 or initiation of chronic dialysis or renal transplant), sustained decrease in eGFR ≥40% relative to baseline, or renal death. Finerenone significantly reduced the risk of the primary composite endpoint [HR:0.825; 95% CI (0.732, 0.928); p=0.0014] (Table 15). The treatment effect reflected a reduction in sustained decreases in eGFR and kidney failure; there were few renal deaths during the trial.

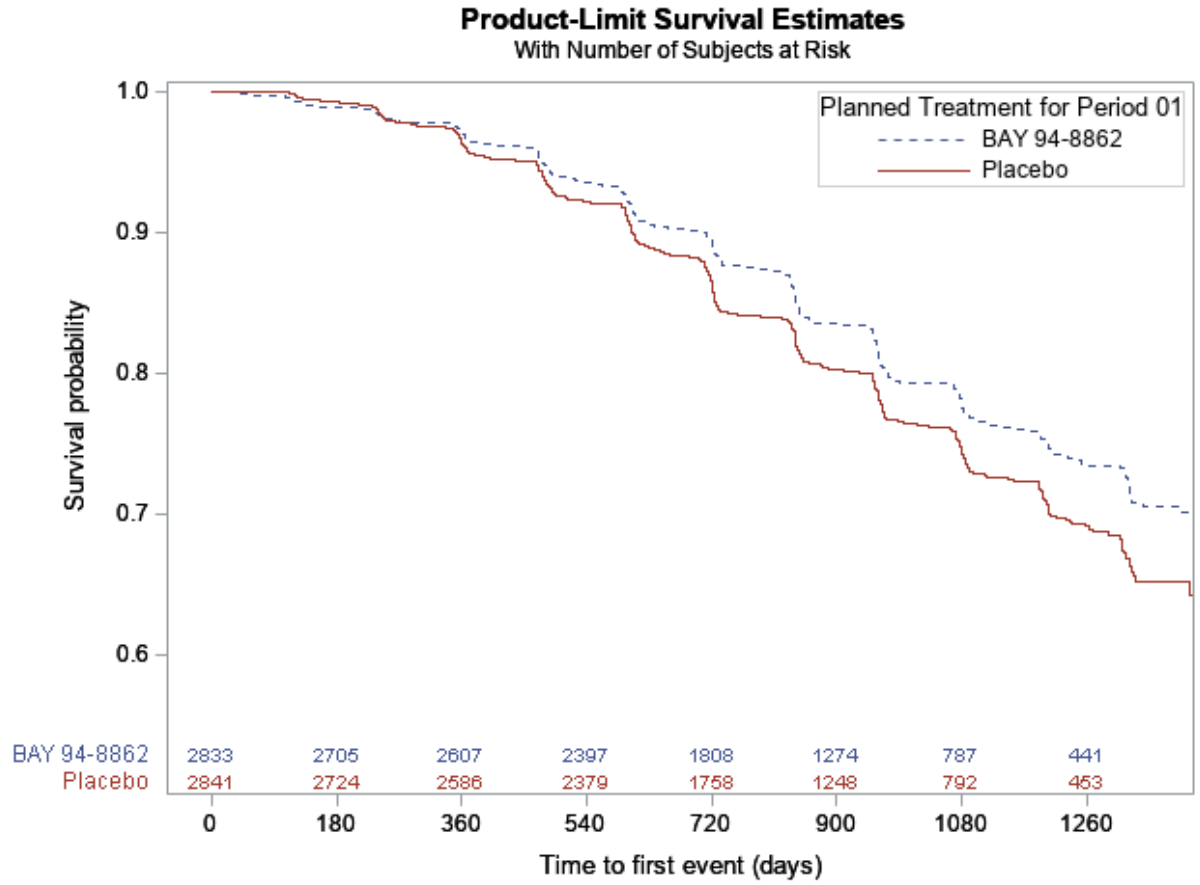
Table 15. Primary Efficacy Analysis (Full Analysis Set)

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	HR (95%CI)	P-value
Primary composite endpoint	504 (17.8%)	600 (21.1%)	0.825 (0.732, 0.928)	0.0014
Kidney failure	89 (3.1%)	82 (2.9%)		
Sustained decrease in eGFR ≥40% (relative to baseline)	477 (16.8%)	571 (20.1%)		
Renal death	0	1 (<0.1%)		
Individual components (all events)				
Kidney failure	208 (7.3%)	235 (8.3%)	0.869 (0.721, 1.048)	
Sustained decrease in eGFR ≥40% (relative to baseline)	479 (16.9%)	577 (20.3%)	0.815 (0.722, 0.920)	
Renal death	2 (<0.1%)	2 (<0.1%)	--	

Source: Applicant's table verified by statistical reviewer. Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; N, number of subjects treated; n, number of subjects in specified population or group

The Kaplan-Meier curves for the primary endpoint separated around month 12 and continued to diverge thereafter (Figure 3; see Section III.16 for KM plots for kidney failure and sustained decrease in eGFR ≥40%). Based on stratified Cox proportional hazards model including treatment by log-transformed time interaction, a p-value of 0.4133 (two-sided) of the interaction term showed no strong evidence against the proportional hazard assumption, which can also be supported from visually examine the curves in the KM plot.

Figure 3. Kaplan-Meier Plot for Primary Event (Full Analysis Set)



Source: generated by statistical reviewer

Missing Data and Sensitivity Analyses

A total of 863 (15%) patients were missing complete data on the primary endpoint (Table 16), i.e., no primary endpoint event was observed in the patient and the patient was censored before the EOS visit. All of these patients were censored prematurely because of missing eGFR assessments. Among them, 405 were censored within four months of the EOS notification date (i.e., they were censored within 4 months of February 3, 2020). The remaining 458 patients were censored at an earlier time point (i.e., before October 3, 2019).

Table 16. Follow-Up of Primary Renal Endpoint (Renal Censoring)

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	Total N=5674 n(%)
Follow up complete	2376 (83.9%)	2435 (85.7%)	4811 (84.8%)
Primary event observed	504 (17.8%)	600 (21.1%)	1104 (19.5%)
Died due to other causes	129 (4.6%)	153 (5.4%)	282 (5.0%)
Censored at EOS[1] visit	1743 (61.5%)	1682 (59.2%)	3425 (60.4%)
Follow up not complete	457 (16.1%)	406 (14.3%)	863 (15.2%)

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	Total N=5674 n(%)
Did not complete treatment /Last eGFR before CDT[2]	229 (8.1%)	192 (6.8%)	421 (7.4%)
Did not complete treatment /Last eGFR after CDT	39 (1.4%)	37 (1.3%)	76 (1.3%)
Complete treatment /Last eGFR before CDT	14 (0.5%)	23 (0.8%)	37 (0.7%)
Complete treatment /Last eGFR after CDT	175(6.2%)	154 (5.4%)	329 (5.8%)

Source: generated by statistical reviewer.
Note: 1. EOS notification visit is 03 Feb 2020; 2. CDT is the cutoff date 4 month before EOS visit.
Abbreviations: CDT, cut-off date; eGFR, estimated glomerular filtration rate; EOS, end of study; N, number of subjects treated; n, number of subjects in specified population or group

Among the 863 patients with incomplete follow-up for the primary renal endpoint, 366 (42%) patients completed treatment. Reasons for not completing treatment, shown in Table 17, were similar in the two arms.

Table 17. Completion of Treatment for Subjects with Incomplete Primary Renal Endpoint Follow-Up

Completion of Treatment	Finerenone N=457 n (%)	Placebo N=406 n (%)	Total N=863 n(%)
Completed	189 (42.4%)	177 (43.6%)	366 (42.4%)
Not completed	268 (56.4%)	229 (58.6%)	497 (57.6%)
Withdrawal by subject	103 (22.5%)	90 (22.2%)	193 (22.4%)
Adverse event / outcome event	77 (16.8%)	64 (15.8%)	141 (16.3%)
Logistical difficulties	29 (6.0%)	24 (5.9%)	53 (6.1%)
Physician decision	25 (5.5%)	21 (5.2%)	46 (5.3%)
Death	10 (2%)	12(2.9%)	22 (2.5%)

Source: generated by statistical reviewer.
Note: categories that are with less than 2% subjects were not shown in this table.
Abbreviations: N, number of subjects treated; n, number of subjects in specified population or group

Because it may not be reasonable to assume all of these data are missing at random, a patient-level worst case imputation and a retrieved dropout based multiple imputation were performed to evaluate the robustness of the primary analysis result. For the patient-level worst case imputation, of the 863 patients with early censoring, 355 patients who did not complete treatment for the reason of "death," "adverse/outcome event," or "withdraw by subject" were each imputed with a primary event at the censor date. For the retrieved dropout based multiple imputation, the unobserved follow-up times of the patients who were censored without a primary efficacy event because of missing eGFR assessments or withdrawal of informed consent were imputed using simulated follow-up times based on annualized hazard rates calculated from retrieved dropouts.[5] Specifically, the hazard rates mentioned above were computed for retrieved dropouts for each treatment arm separately. A Weibull distribution was used for modelling the time from the last dose date to either the primary efficacy event or censored date, then the simulated follow-up times were added to the observed censoring date to obtain the imputed time to event for those patients who were censored early. If the imputed time to event was before the cut-off date, the patient "experienced" the primary endpoint event at the imputed time; if not, the patient would

[5] For the purpose of this analysis, patients who prematurely discontinued the study treatment and either stayed in the study until a primary event was observed or were censored due to study completion or death were considered to be "retrieved dropouts;" patients who experienced the primary efficacy endpoint prior to the treatment discontinuation date were thus not considered "retrieved dropouts."

be censored at the cut-off date. As shown in Table 18, the results of these analyses were consistent with the primary analysis, indicating that the primary endpoint results were robust to various assumptions about the missing data.

Table 18. Sensitivity Analyses for Primary Renal Endpoint

Analyses	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	HR (95%CI)	P-value
Patient-level worst case imputation	694	765	0.89 (0.81, 0.99)	0.0312
Analyses	Mean number of subjects with efficacy outcome		MI HR (96.717%CI)	-
Retrieved dropout-based MI	619.9	712.2	0.85 (0.75, 0.96)	-

Source: patient-level worst case imputation was performed by statistical reviewer. Retrieved dropout MI was from Applicant's response to Information Request 11 and verified by statistical reviewer.
Abbreviations: CI, confidence interval; HR, hazard ratio; MI, multiple imputation; N, number of subjects treated; n, number of subjects in specified population or group

Analysis of Key Secondary Endpoint

The "key" secondary endpoint was the time to the first occurrence of the following CV composite endpoint: CV death, non-fatal MI, non-fatal stroke, or hospitalization for heart failure. As such in Table 19, fewer patients in the finerenone arm experienced an event as compared to the placebo arm [HR: 0.860; 95%CI (0.747, 0.989)].

According to the prespecified testing procedure, since the primary endpoint was statistically significant, the key secondary endpoint was tested at a significance level at 0.0497. The key secondary composite endpoint reached statistical significance with a p-value of 0.0339 based on the log rank test. All components, with the exception of non-fatal stroke, contributed to the effect.

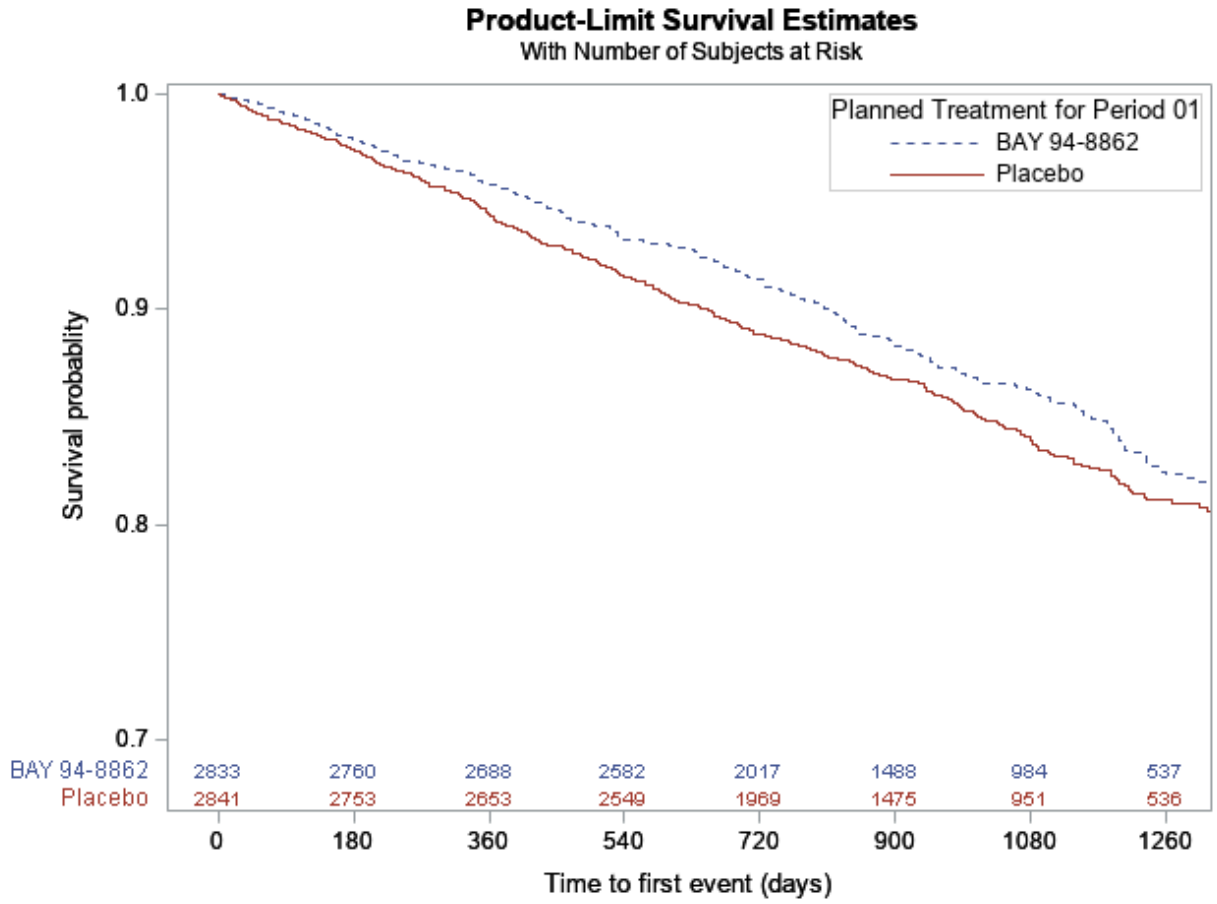
Table 19. Key Secondary Efficacy Analysis

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	HR (95%CI)	P-value
Key secondary composite endpoint	367 (13.0%)	420 (14.8%)	0.860 (0.747, 0.989)	0.0339
CV death	98 (3.5%)	115 (4.0%)		
Non-fatal MI	65 (2.3%)	82 (2.9%)		
Non-fatal stroke	81 (2.9%)	80 (2.8%)		
Hospitalization due to heart failure	124 (4.4%)	146 (5.1%)		
Individual components (all events)				
CV death	128 (4.5%)	150 (5.3%)	0.855 (0.675, 1.083)	
Non-fatal MI	70 (2.5%)	87 (3.1%)	0.796 (0.581, 1.090)	
Non-fatal stroke	90 (3.2%)	87 (3.1%)	1.027 (0.765, 1.380)	
Hospitalization due to heart failure	139 (1.9%)	162 (5.7%)	0.857 (0.683, 1.076)	

Source: Applicant's table verified by statistical reviewer. Analyses of the components of the key secondary composite endpoint were not prospectively planned to be adjusted for multiplicity.
Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; N, number of subjects treated; n, number of subjects in specified population or group

The Kaplan-Meier curves for the key secondary endpoint separated early in the trial (Figure 4). See Section III.16 for the Kaplan-Meier plots for the components of the secondary CV composite endpoint.

Figure 4. Kaplan-Meier Plot for Key Secondary Event (Full Analysis Set)



Source: generated by statistical reviewer.

Additional analyses were conducted to evaluate the findings for the stroke endpoint. As shown in Table 20, there were few fatal strokes and findings for total strokes (both fatal and non-fatal) were similar to those for non-fatal stroke (i.e., the analysis did not suggest a treatment effect on stroke).

Table 20. Analysis of Fatal/Non-Fatal Stroke

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	HR (95%CI)	P-value
Fatal stroke	12 (0.4%)	12 (0.4%)	1.003 (0.450; 2.232)	0.9948
Hemorrhagic	3	5		
Ischemic	9	7		
Non-fatal stroke	90 (3.2%)	87 (3.1%)	1.027 (0.765; 1.380)	0.8579
Hemorrhagic	5	9		
Ischemic	85	78		
All types of stroke	102 (3.6%)	99 (3.5%)	1.024 (0.776; 1.350)	0.8672

Source: generated by statistical reviewer.
Abbreviations: CI, confidence interval; HR, hazard ratio; N, number of subjects treated; n, number of subjects in specified population or group

Analysis of Other Secondary Endpoints

The remaining four secondary endpoints were tested hierarchically in the prespecified order. The first endpoint in the sequence was all-cause mortality. This endpoint did not reach statistical significance (p-value of 0.23); thus, the remaining secondary endpoints were considered to be exploratory and were not formally tested. Results are shown in Table 21.

Table 21. Other Secondary Efficacy Analyses

Endpoint	Finerenone N=2833 n (%)	Placebo N=2841 n (%)	HR (95%CI)	P-value
All-cause mortality	219 (7.7%)	244 (8.6%)	0.895 (0.746, 1.075)	0.2348
CV death	128 (4.5%)	150 (5.3%)	0.855 (0.675, 1.083)	
Renal death	2 (<0.1%)	2 (<0.1%)	-	
Fatal, non-CV/non-renal	89 (3.1%)	92 (3.2%)	0.958 (0.716, 1.283)	
All-cause hospitalization	1263 (44.6%)	1321 (16.5%)	0.946 (0.876, 1.022)	
Change in UACR from baseline to Month 4	LS-mean 0.655	LS-mean 0.952	Ratio of LS-means 0.688 (0.662, 0.715)	
Secondary Renal Composite Endpoint	252 (8.9%)	326 (11.5%)	0.763 (0.648, 0.900)	

Source: Applicant's table verified by statistical reviewer.
Abbreviations: CI, confidence interval; CV, cardiovascular; HR, hazard ratio; N, number of patients treated; n, number of patients in specified population or group; UACR, urine albumin-to-creatinine ratio

Subgroup Analyses

Subgroup analyses of the primary renal composite endpoint were performed on pre-specified subgroups. Figure 5 and Figure 6 show the subgroup analyses that were verified by the statistical reviewer. Hazard ratios (95% CI) and interaction 2-sided p-values were based on stratified Cox proportional hazards models including treatment, subgroup, and subgroup by treatment interaction terms as fixed effects**.**

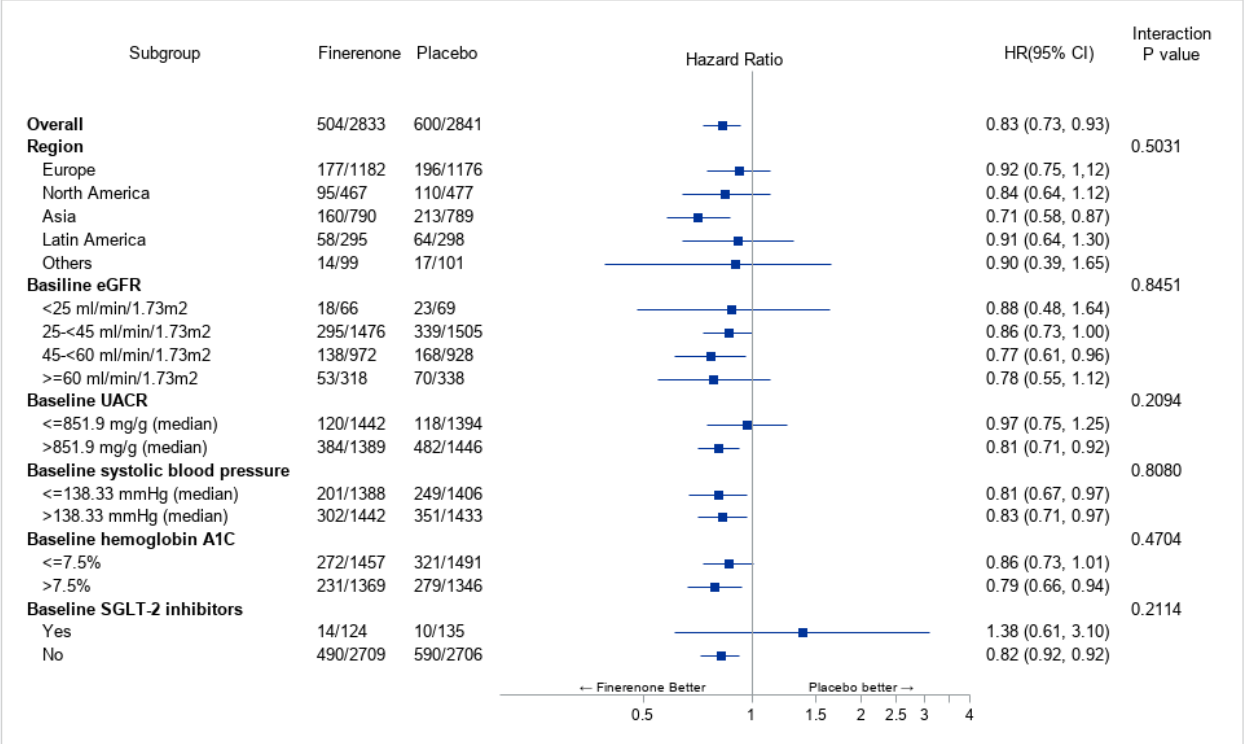
An interaction test for homogeneity suggested that there was heterogeneity wit**h respect to the treatment effect of finerenone across the subgroup categories of the following variables:**

- History of CV disease (interaction p-value 0.0160): HRs were 0.70 for patients with CV disease present at baseline and 0.94 for patients with CV disease absent**.**
- Baseline BMI (interaction p-values of 0.0028): HRs were 0.68 for patients with a BMI <30 kg/m^2 and 0.98 for patients with a BMI ≥30 kg/m^2**.**

More granular subcategorizations in which patients were divided into 4 to 5 BMI categories did not indicate a clear BMI-response relationship across all levels of BMI though still raised questions about diminished efficacy at higher BMIs. As such, an IR was sent to the Applicant and further analyses were conducted. Analyses did not indicate meaningful differences in exposure among the BMI subgroups and neither the CV composite endpoint nor the UACR endpoint showed heterogeneity across BMI categories. Hence, both the Applicant and review team concluded that the observed subgroup finding was unlikely to represent true heterogeneity of the treatment effect.

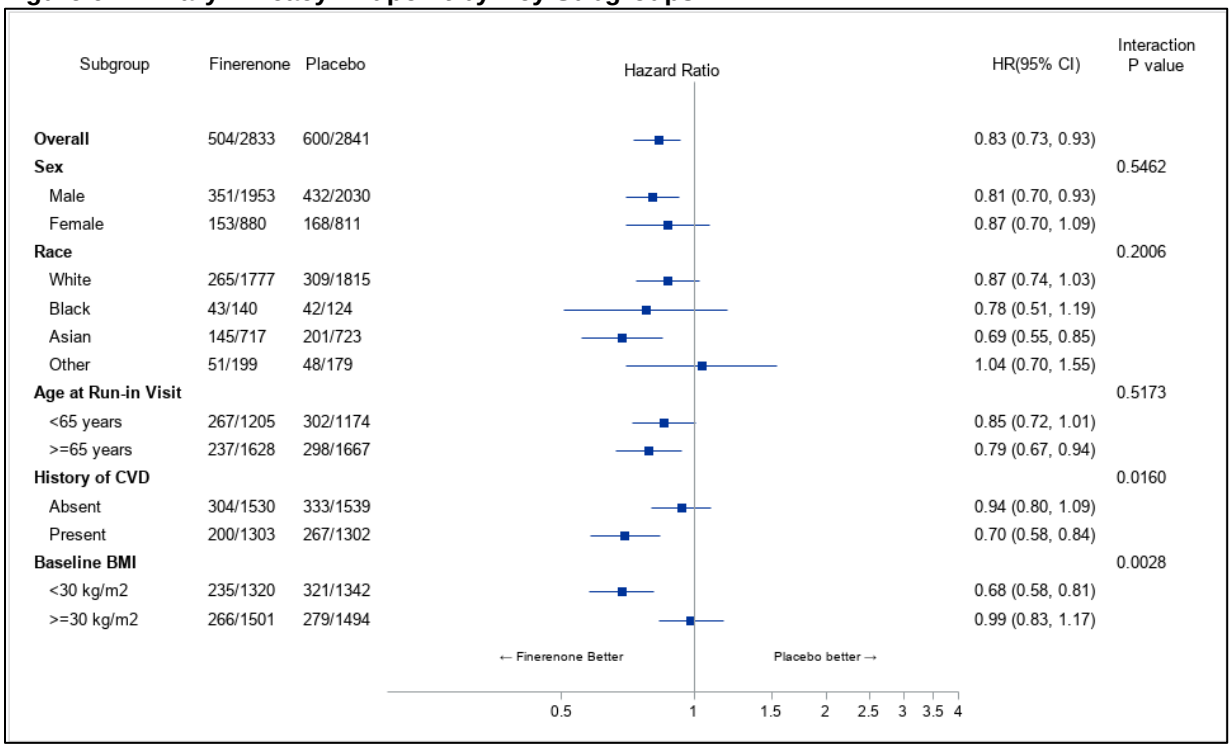
There were too few patients on SGLT-2 inhibitors at baseline to draw meaningful conclusions.

Figure 5. Primary Efficacy Endpoint by Regional Subgroups



Source: generated by statistical reviewer.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, albumin-to-creatinine ratio

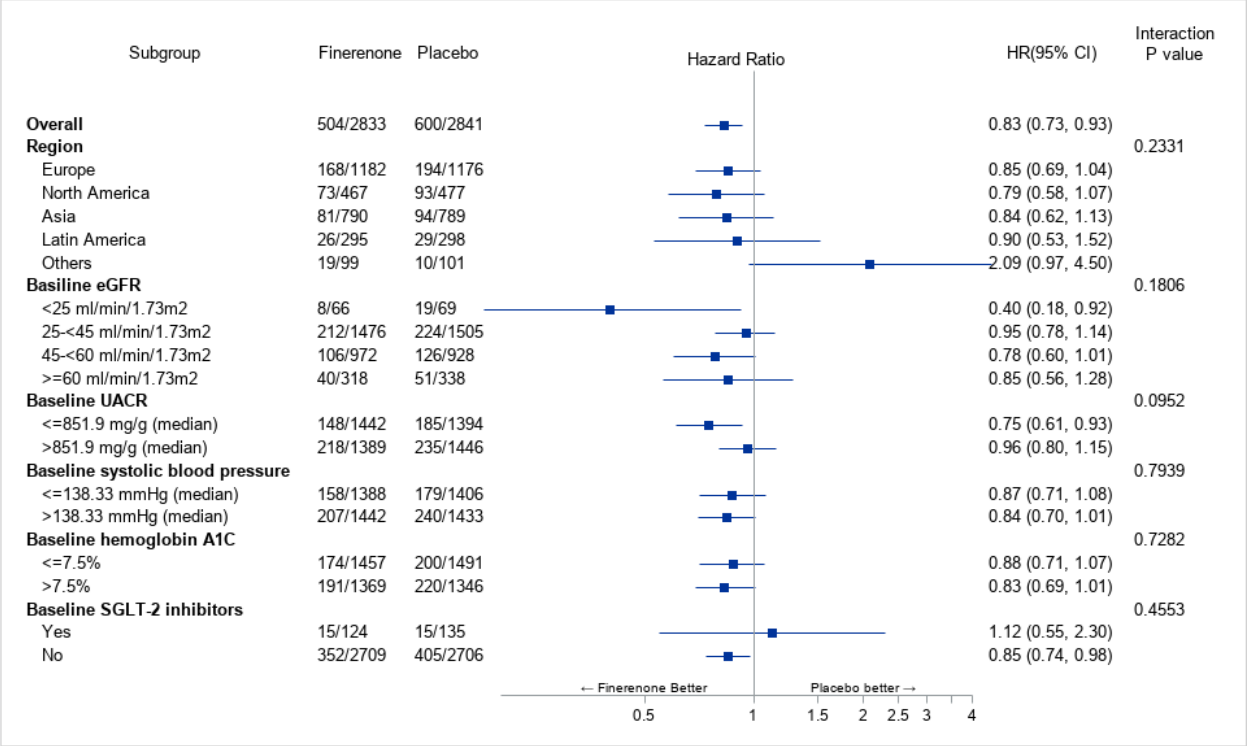
Figure 6. Primary Efficacy Endpoint by Key Subgroups



Source: generated by statistical reviewer.
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio

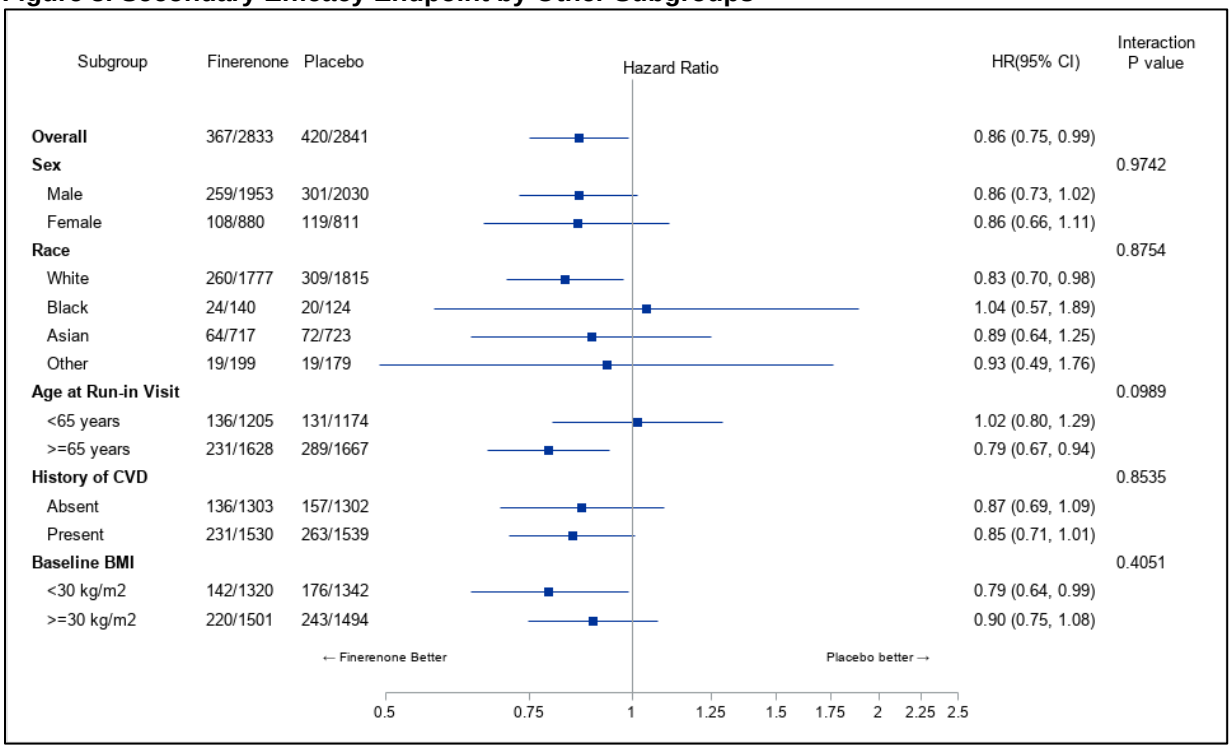
For the key secondary CV composite endpoint, exploratory tests for interaction did not suggest obvious differences in the treatment effect among the tested subgroups (Figure 7 and Figure 8). There were too few patients on SGLT-2 inhibitors at baseline to draw meaningful conclusions.

Figure 7. Secondary Efficacy Endpoint by Regional Subgroups



Source: generated by statistical reviewer.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; UACR, albumin-to-creatinine ratio

Figure 8. Secondary Efficacy Endpoint by Other Subgroups



Source: generated by statistical reviewer.
Abbreviations: BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio

6.3. Key Review Issues Relevant to Evaluation of Benefit

There are no issues related to the evaluation of benefit that warrant discussion in this section.

7. Risk and Risk Management

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Studies performed to assess the safety of finerenone in animals included a full battery of safety pharmacology studies (including the human ether-a-go-go-related gene (hERG) assay), a full battery of genetic toxicology studies, general toxicology studies up to 6 months in the rat and up to 9 months in the dog, a full battery of reproductive toxicology studies (including a fertility and early embryonic development study in rat, embryofetal developmental toxicity studies in rat and rabbit and a pre-and postnatal development study in rat), and two 2-year carcinogenicity studies in mouse and rat. In the dog 9-month study, the disproportionate human metabolite M-1 was qualified. Nonclinical support for administration of finerenone to pediatric patients down to 6 months of age is provided by a 13-week general juvenile toxicology study and a juvenile reproductive toxicology study in female rats. There were no nonclinical safety issues of concern identified by these studies. All pertinent studies and findings are summarized in the following section. All nonclinical studies submitted under the IND are tabulated and are located in Section III.13.1 of this document. Full reviews for the two carcinogenicity studies are located in Section III.13.2 of this document.

In sum, from a pharmacology/toxicology perspective, the nonclinical safety assessment for finerenone is acceptable to support approval for the proposed indication.

Safety Pharmacology, Secondary Pharmacology**,** and Pharmacokinetics/ADME

In safety pharmacology studies, finerenone was tested in GLP compliant, core battery studies according to the ICH S7A and S7B guidelines. Finerenone showed no adverse effects on CNS parameters and respiratory functions (rat), on hemodynamic/ECG parameters (dog), and on cardiac repolarization in vitro (hERG K+ current). The only noteworthy finding was a slightly accelerated atrioventricular conduction evidenced by a shortening of the PQ interval in the dog cardiac safety study seen at doses ≥3 mg/kg. NOAEL was considered to be 1 mg/kg, corresponding to maximal plasma concentrations of 1.4 mg/L (C_{max}-unbound 77 µg/L; fu 5.5%); this concentration exceeds the C_{max} at MRHD by about 7-fold.

A secondary pharmacology screening with finerenone revealed no potential for off-target liability. The major human metabolites (M1, M2 and M3) were also tested for off-target binding as well as interaction with cardiac ion channels in vitro and showed no effect.

The pharmacokinetics of finerenone were investigated in vivo in animal studies and in humans. Additionally, in vitro studies were performed to investigate plasma protein binding, blood/plasma partitioning, drug-drug-interaction potential, drug metabolism in several species including humans, and transporter characteristics, including interaction potential.

Finerenone shows a moderate to high bioavailability in nonclinical species, ranging from 83 to 120% in rats and 57 to 100% in dogs. A higher exposure was reported in female rats compared to male rats, but no sex-dependent pharmacokinetic differences in dogs.

Pronounced differences in plasma protein binding were shown between rodent and nonrodent species. The binding to plasma proteins is very high in rodent species, moderate to high in non-rodent (monkey, dog) and humans with the fraction unbound (fu) ranging from 0.047% (Wistar rat) to 8.3% (human). In human plasma, the naphthyridine metabolites M-1, M-2, and M-3 were the predominant metabolites in this order covering, 49%, 22%, and 9% of the area under the curve (AUC) of total radioactivity. All three metabolites were shown to be pharmacologically inactive against human mineralocorticoid receptor. There is no unique human metabolite, but M1 and M3 were shown to be disproportionately higher in human plasma following a single oral administration. Oxidative metabolism of finerenone was predominantly catalyzed by CYP3A4 with minor contribution of CYP2C8.

Detailed investigations revealed that the predominant human plasma metabolites M-1, M-2, and M-3 exhibited axial chirality forming the atropisomers BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a), BAY 1117270 (M-2b), BAY 1117271 (M-3a) and BAY 1117272 (M-3b). Analysis of plasma and urine samples of rat, dog and human after single/multiple dose administration of [14C]finerenone/finerenone revealed the predominant appearance of one atropisomer (a-series, >80%) of each metabolite across all species. In vivo results are well reflected by in vitro investigations in liver microsomes. Based on a human mass balance study, metabolites M-1a, M-1b, M-2a can be regarded as major human plasma metabolites (accounting for >10% of AUC of total radioactivity), whereas M-2b, M-3a and M-3b are regarded as minor metabolites in healthy subjects. Furthermore, based on exposure data of M-3 in renal impaired patients and atropisomer ratios, calculations revealed M-3a to be an additional major metabolite in humans with impaired kidney function. The disproportionate M-1

metabolite, which is also a major human metabolite observed at exposure greater than 10% of total drug-related exposure, was qualified in the 9-month dog general toxicology study.

General Toxicology (Pivotal Studies)

In GLP chronic toxicity studies, findings mostly reflect the intended mode of action resulting in exaggerated pharmacology and sequelae thereof. Clinical effects included increased water intake, reduced body weight gain as well as mild impairment of electrolyte levels (increase in potassium and calcium, decrease in sodium and chloride). Target organs of exaggerated pharmacology after chronic treatment were the adrenals in both the rat and dog and also the prostate in the dog (decrease in prostate size and weight not accompanied by histopathological changes).

In the 4-week and 13-week general toxicity studies in rats, pituitary, lacrimal glands, liver, kidney, urinary bladder, and female genital tract were also affected at high doses. All findings were fully or at least partially reversible except for mineralization in the kidneys of females and urinary bladder hyperplasia in males at 30 mg/kg. The findings in the kidney and urinary tract were considered to be secondary to the pharmacological effect of finerenone on electrolyte balance and urinary volume. Other noteworthy findings included effects on female reproductive organs (foamy corpora lutea cells in the ovary, endometrial and myometrial atrophy in the uterus and epithelial atrophy or alteration in the vagina), findings that are indicative of hormonal imbalance. The adverse findings in the kidney and female reproductive organs were not observed in the chronic toxicity study in rats, which evaluated lower dose levels.

The safety margins based on the exposures at NOAELs in the pivotal chronic toxicity studies are summarized in Table 22 and Table 23.

Table 22. Rat 6-Month Toxicity Safety Margin

Study	NOAEL (mg/kg)	Nonclinical Exposure-Total (µM•hr/L)	Nonclinical Exposure-Unbound (µM•hr/L)	Safety Margins*
Males	5	704000	327	308X (6X)
Females	1.5	992000	461	435X (8X)

Source: Generated by pharmacology/toxicology reviewer
* Exposure multiples were based on population pharmacokinetics analysis where a 20 mg QD clinical dose resulted in a mean systemic exposure of $AUC_{0\text{-}24hr}$ =686 µg•hr/L and
$AUC_{0\text{-}24hr\ unbound}$ =57 µg•hr/mL (fu =8.33%). The free fractions (fu) is 0.0465% in rat plasma. The safety margin calculation was based on both total AUC and unbound AUC (in parentheses).
Abbreviations: AUC, area under the curve; NOAEL, no observable adverse effect level

Table 23. Canine 9-Month Toxicity Safety Margin

Study	NOAEL (mg/kg)	Nonclinical Exposure-Total (µM•hr/L)	Nonclinical Exposure-Unbound (µM•hr/L)	Safety Margins*
Males	0.5	2110	116	3X (2X)
Females	5	59500	3267	86X (57X)

Source: Generated by pharmacology/toxicology reviewer
* Exposure multiples were based on population pharmacokinetics analysis where a 20 mg QD clinical dose resulted in a mean systemic exposure of $AUC_{0\text{-}24hr}$ =686 µg•hr/L and
$AUC_{0\text{-}24hr}$ unbound =57 µg•hr/mL (fu =8.33%). The free fractions (fu) is 5.49% in dog plasma. The safety margin calculation was based on both total AUC and unbound AUC (in parentheses).
Abbreviations: AUC, area under the curve; NOAEL, no observable adverse effect level

Genetic Toxicology and Carcinogenicity

Finerenone was tested in a standard battery of GLP-compliant genotoxicity assays in line with ICH-S2(R1) guidelines. Under the experimental conditions reported, finerenone did not induce gene mutations by base-pair changes or frame-shifts in the genome of five *S. typhimurium* strains when tested up to a maximum recommended dose of 5.0 mg/plate in the absence and presence of S9 mix. Finerenone was also negative in the in vitro chromosomal aberration assay in mammalian cells and in the in vivo mouse micronucleus test. Two-year carcinogenicity studies conducted in mice and rats showed no significant increase in neoplasms in males or females in either study; the CDER Exec CAC concurred with this conclusion. These studies are reviewed in detail in Section III.13.2 of this document.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Approved mineralocorticoid receptor antagonists include spironolactone and eplerenone. Warnings and Precautions listed in the current labels for these drugs that are relevant to finerenone include: hyperkalemia for both spironolactone and eplerenone, and hypotension and worsening renal function, electrolyte, and metabolic abnormalities (e.g., hyponatremia), and gynecomastia for spironolactone.

7.3. Potential Safety Concerns Identified Through Postmarket Experience

This drug has not yet been marketed.

7.4. FDA Approach to the Safety Review

Anne Bunner and Jinzhong Liu conducted the safety analyses presented in this review. The safety section of this review was drafted by Rekha Kambhampati.

The safety evaluation focused on the FIDELIO-DKD study, the pivotal phase 3 trial. The safety review included a review of data quality and integrity,[6] as well as adverse event and laboratory datasets. No major issues were identified with respect to recording, coding, and categorizing AEs. The Applicant's translation of verbatim terms to MedDRA preferred terms for the events reported in the study was reviewed and found to be acceptable.

Safety analyses used the Safety Analysis Population, which consisted of patients who received at least one dose of study drug. Adverse events that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug were considered as treatment-emergent adverse events (TEAEs). The protocol did not pre-specify Adverse Events of Special Interest. The safety review of FIDELIO-DKD focused on the known risks of MRAs, including hyperkalemia, hypotension, AKI, hyponatremia, and gynecomastia. Adverse events were analyzed by MedDRA version 23.0 preferred term (similar to the Applicant's analyses) and by pooling similar adverse events (referred to as the FDA Medical Dictionary for Regulatory Activities [MedDRA]Query [FMQ]). For adverse events in which an FMQ was not available

[6] Data integrity was examined using the Office of Computational Science Core Data Fitness

(e.g., hyperkalemia, hyponatremia), preferred terms were grouped, similar to a customized MedDRA query.

7.5. Adequacy of Clinical Safety Database

The size of the safety database and duration of exposure are considered adequate to characterize safety in the proposed population. The mean duration of finerenone exposure in the FIDELIO-DKD trial was 26.9 months; see Table 24 for additional information on the duration of exposure in FIDELIO-DKD.

Table 24. Duration of Exposure, Safety Population, Trial 16244

Variable	Finerenone N=2827 n (%)	Placebo N=2831 n (%)
Duration of treatment (months)		
Mean (SD)	26.9 (12.4)	27.3 (12.1)
Median (Q1, Q3)	27.1 (19.6, 36.3)	27.2 (20, 36.2)
Min, Max	0, 51.5	0.1, 51.5
Subjects treated, by duration, n (%)		
<12 months	381 (13.5)	359 (12.7)
≥12 months	2446 (86.5)	2472 (87.3)
≥24 months	1631 (57.7)	1661 (58.7)
≥36 months	724 (25.6)	718 (25.4)

Source: adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; SD, standard deviation

7.6. Safety Findings and Concerns Based on Review of Clinical Safety Database

7.6.1. Safety Findings and Concerns

7.6.1.1. Overall Treatment-Emergent Adverse Event Summary

The overall incidence of adverse events was similar in the two arms in FIDELIO-DKD. Most AEs were reported to be moderate or severe (Table 25). There was a greater incidence of AEs leading to discontinuation or dose modification of study drug in the finerenone arm as compared to the placebo arm (see Section 7.6.1.4 for further details). In contrast, the incidence of serious adverse events (SAEs) and SAEs with a fatal outcome was slightly numerically greater in the placebo arm as compared to the finerenone arm.

Table 25. Overview of Adverse Events, Safety Population, Trial 16244

Event Category	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Any AE	2468 (87.3)	2478 (87.5)	-0.2 (-1.9, 1.5)
Moderate or severe AEs	1646 (58.2)	1714 (60.5)	-2.3 (-4.9, 0.3)
Any SAE	902 (31.9)	971 (34.3)	-2.4 (-4.9, 0.1)
SAE with fatal outcome	31 (1.1)	51 (1.8)	-0.6 (-1.2, 0.0)
AE leading to discontinuation of study drug	207 (7.3)	168 (5.9)	1.4 (0.1, 2.7)

Event Category	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
AE leading to dose modification of study drug	770 (27.2)	597 (21.1)	6.1 (3.9, 8.3)
AE leading to interruption of study drug	734 (26.0)	567 (20.0)	6.0 (3.8, 8.2)
AE leading to reduction of study drug	63 (2.2)	48 (1.7)	0.5 (-0.2, 1.2)
AE leading to delay of study drug	0	0	0.0 (0.0, 0.0)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths

As discussed in Section III.15, all deaths in FIDELIO-DKD were adjudicated. All-cause mortality was lower in the finerenone (7.7%) as compared to the placebo (8.6%) arm. As seen in Table 26, in both arms, most deaths were cardiovascular (4.5% finerenone, 5.3% placebo), with the most common adjudicated causes being sudden cardiac death or "undetermined." All other cardiovascular deaths occurred at an incidence of ≤1% in either arm. There were only 2 adjudicated renal deaths in each arm (<0.1% for each arm). As shown in Table 26, the incidence of non-cardiovascular and non-renal deaths were similar in the two arms (1.3% finerenone versus 1.2% placebo). In both arms, infection and malignancy were the most common adjudicated causes of non-cardiovascular and non-renal deaths, with all other causes occurring at an incidence of ≤1% in either arm.

Table 26. Adjudicated Reasons for Deaths That Occurred at >1% Incidence in Any Arm, Safety Population, Trial 16244

Preferred Term	Finerenone N=2827 n (%)	Placebo N=2831 n (%)
Death from any cause	217 (7.7)	243 (8.6)
Cardiovascular death	126 (4.5)	149 (5.3)
Sudden cardiac death	35 (1.2)	42 (1.5)
Undetermined	54 (1.9)	67 (2.4)
Non-cardiovascular/non-renal deaths	89 (3.1)	92 (3.2)
Infection	37 (1.3)	35 (1.2)
Malignancy	31 (1.1)	31 (1.1)

Source: Clinical Study Report, Table 10-12; verified by FDA
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.3. Serious Adverse Events

MedDRA Preferred Term Analysis

The overall incidence of SAEs was slightly numerically higher in the placebo arm as compared to the finerenone arm in FIDELIO-DKD (32% and 34% of patients, respectively). Table 27 shows SAEs that were reported in at least 1% of patients in either arm. Unless otherwise indicated, preferred terms were not pooled for the purpose of this analysis; analyses pooling preferred terms that capture a similar medical concept are discussed in the subsequent section.

As shown in Table 27, hyperkalemia[7] SAEs were reported at a higher incidence in patients on finerenone (1.6%) compared to placebo (0.4%) (see Section 7.6.1.6 for details). The incidence of acute kidney injury (AKI) SAEs was similar in the two arms (2.0% finerenone and 1.8% placebo; see Section 7.6.1.6 for details). SAEs related to hypotension (0.2% in each arm) and hyponatremia[8] (0.3% for finerenone versus 0.04% for placebo) were uncommon in both arms. No SAEs were reported at an incidence at least 2% greater in the finerenone arm as compared to the placebo arm.

Table 27. Serious Adverse Events Occurring in at Least 1% of Patients in Any Arm, Safety Population, Trial 16244

Preferred Term	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Any SAE	902 (31.9)	971 (34.3)	-2.4 (-4.9, 0.1)
Acute kidney injury	56 (2.0)	51 (1.8)	0.2 (-0.5, 0.9)
Hyperkalaemia[2]	44 (1.6)	12 (0.4)	1.1 (0.6, 1.6)
Hypoglycaemia	21 (0.7)	31 (1.1)	-0.4 (-0.9, 0.1)
Pneumonia	70 (2.5)	103 (3.6)	-1.1 (-2.0, -0.2)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
[2]Includes hyperkalaemia and blood potassium increased
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

Narrow FDA MedDRA Query (FMQ) Analysis

The results of analyses obtained using FDA MedDRA Queries (narrow) are shown in Table 28. SAEs consistent with hemorrhage (narrow FMQ) were reported at a greater incidence in the finerenone as compared to the placebo arm (2.2% vs 1.3%, respectively); however, the incidence of all TEAEs of hemorrhage (narrow FMQ) was the same in the two arms (7.9%), and hemorrhage was not observed in general toxicology studies. SAEs consistent with malignancy (narrow FMQ) were also reported at a slightly greater incidence in the finerenone (3.0%) as compared to the placebo arm (2.5%). As discussed later in this review, concerning findings were not observed in genetic toxicology and preclinical carcinogenicity studies. Absent a clear mechanistic basis for this imbalance, the significance is unclear.

The incidence of SAEs suggestive of AKI (narrow FMQ) was similar in the two arms (see Section 7.6.1.6 for details), as was the incidence of SAEs of hypotension (narrow FMQ; 0.4% finerenone versus 0.2% placebo). Custom grouped queries were used to assess for SAEs of hyperkalemia and hyponatremia since FMQs do not exist for these medical conditions; see the prior section for the results.

[7] Includes the preferred terms blood potassium increased and hyperkalaemia
[8] Includes the preferred terms blood sodium decreased and hyponatraemia

Table 28. SAEs by FDA MedDRA Query (Narrow) Occurring in at Least 1% of Patients in Any Arm and Preferred Terms Occurring in at Least 0.5% of Patients in Any Arm, Safety Population, Trial 16244

FMQ (Narrow) Preferred Term	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Malignancy (narrow FMQ)	84 (3.0)	71 (2.5)	0.5 (-0.4, 1.4)
Prostate cancer	13 (0.5)	5 (0.2)	0.3 (0.0, 0.6)
Haemorrhage (narrow FMQ)	62 (2.2)	37 (1.3)	0.9 (0.2, 1.6)
Gastrointestinal haemorrhage	13 (0.5)	7 (0.2)	0.3 (-0.0, 0.6)
Acute kidney injury (narrow FMQ)	57 (2.0)	53 (1.9)	0.1 (-0.6, 0.8)
Acute kidney injury	56 (2.0)	51 (1.8)	0.2 (-0.5, 0.9)
Arthritis (narrow FMQ)	25 (0.9)	27 (1.0)	-0.1 (-0.6, 0.4)
Hypoglycaemia (narrow FMQ)	22 (0.8)	31 (1.1)	-0.3 (-0.8, 0.2)
Hypoglycaemia	21 (0.7)	31 (1.1)	-0.4 (-0.9, 0.1)
Anaemia (narrow FMQ)	23 (0.8)	34 (1.2)	-0.4 (-0.9, 0.1)
Anaemia	14 (0.5)	19 (0.7)	-0.2 (-0.6, 0.2)
Systemic hypertension (narrow FMQ)	21 (0.7)	37 (1.3)	-0.6 (-1.1, -0.1)
Hypertension	15 (0.5)	23 (0.8)	-0.3 (-0.7, 0.1)
Pneumonia (narrow FMQ)	78 (2.8)	118 (4.2)	-1.4 (-2.4, -0.4)
Pneumonia	70 (2.5)	103 (3.6)	-1.1 (-2.0, -0.2)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAEs, serious adverse events

7.6.1.4. Medication Discontinuations Due to Adverse Events

Approximately 7% of patients in the finerenone arm and 6% of patients in the placebo arm in FIDELIO-DKD discontinued study drug due to an AE. The most common reason for medication discontinuation in both arms was hyperkalemia[7] as discussed in Section III.15, the protocol included guidelines for discontinuation of study drug based on serum potassium thresholds. The proportion of patients who discontinued study drug because of hyperkalemia was higher in the finerenone (2.3%) as compared to the placebo (0.9%) arm. With the exception of hyperkalemia, the proportion of patients who discontinued study drug due to any single AE was low (≤0.3%) in both arms. There were no narrow FMQs for which the incidence risk difference (IRD) for medication discontinuation was ≥1% for finerenone compared to placebo.

7.6.1.5. Treatment-Emergent Adverse Events

TEAEs that occurred in at least 2% of patients in any arm and had an IRD of at least 1% between arms in FIDELIO-DKD are shown in Table 29; consistent with the mechanism of action of finerenone, there was a higher incidence of the AEs of hyperkalemia,[7] glomerular filtration rate decreased, and hypotension for finerenone compared to placebo. There was also a slightly higher incidence of pruritis for patients on finerenone (3.7%) compared to placebo (2.6%); however, there was no clear mechanistic basis for this finding and other analyses did not suggest a signal. Consistent with the mechanism of action of finerenone, the incidence of TEAEs of hyponatremia[8] was higher in the finerenone (1.4%) as compared to the placebo (0.7%) arm.

There was also a slightly higher incidence of dehydration[9] for finerenone (1.7%) compared to placebo (1.2%). TEAEs of gynecomastia were uncommon in both arms (<0.5%).

Table 29. Adverse Events by System Organ Class and Preferred Term, Showing Terms Occurring in at Least 2% of Patients in Any Arm and With a Risk Difference of at least 1% Between Arms, Safety Population, Trial 16244

System Organ Class Preferred Term	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Metabolism and nutrition disorders (SOC)	1045 (37.0)	958 (33.8)	3.2 (0.7, 5.7)
Hyperkalaemia[2]	516 (18.3)	255 (9.0)	9.3 (7.5, 11)
Hypoglycaemia	151 (5.3)	194 (6.9)	-1.6 (-2.8, -0.4)
Hypokalaemia	28 (1.0)	61 (2.2)	-1.2 (-1.8, -0.6)
Investigations (SOC)	649 (23.0)	682 (24.1)	-1.1 (-3.3, 1.1)
Glomerular filtration rate decreased	179 (6.3)	133 (4.7)	1.6 (0.4, 2.8)
Blood creatine phosphokinase increased	64 (2.3)	102 (3.6)	-1.3 (-2.2, -0.4)
Vascular disorders (SOC)	537 (19.0)	537 (19.0)	0.0 (-2.0, 2.0)
Hypotension	126 (4.5)	87 (3.1)	1.4 (0.4, 2.4)
Hypertension	212 (7.5)	273 (9.6)	-2.1 (-3.6, -0.6)
Skin and subcutaneous tissue disorders (SOC)	450 (15.9)	452 (16.0)	-0.1 (-2.0, 1.8)
Pruritus	104 (3.7)	73 (2.6)	1.1 (0.2, 2.0)
Infections and infestations (SOC)	1227 (43.4)	1255 (44.3)	-0.9 (-3.5, 1.7)
Pneumonia	128 (4.5)	181 (6.4)	-1.9 (-3.1, -0.7)
Gastrointestinal disorders (SOC)	747 (26.4)	772 (27.3)	-0.9 (-3.2, 1.4)
Constipation	131 (4.6)	163 (5.8)	-1.2 (-2.4, -0.0)
General disorders and administration site conditions (SOC)	512 (18.1)	645 (22.8)	-4.7 (-6.8, -2.6)
Oedema peripheral	186 (6.6)	304 (10.7)	-4.1 (-5.6, -2.6)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator
[2]Includes hyperkalaemia and blood potassium increased
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

The results of the MedDRA Preferred Term analysis and associated FMQ analyses were generally consistent with each other. In an analysis using the narrow FMQ for gynecomastia, the incidence of AEs suggestive of gynecomastia was not greater in the finerenone as compared to the placebo arm.

Table 30 shows AEs by narrow FMQ with an IRD of ≥1% between arms.

Table 30. Adverse Events by FDA MedDRA Query (Narrow) With a Risk Difference of ≥1% Between Arms, Safety Population, Trial 16244

FDA MedDRA Query (Narrow)	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Hypotension (narrow FMQ)	151 (5.3)	111 (3.9)	1.4 (0.3, 2.5)
Pruritus (narrow FMQ)	116 (4.1)	85 (3.0)	1.1 (0.1, 2.1)
Constipation (narrow FMQ)	131 (4.6)	163 (5.8)	-1.2 (-2.4, -0.0)
Hypoglycaemia (narrow FMQ)	156 (5.5)	195 (6.9)	-1.4 (-2.7, -0.1)

[9] Includes the preferred terms dehydration, hypovolemia, and hypovolemic shock

FDA MedDRA Query (Narrow)	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Pneumonia (narrow FMQ)	142 (5.0)	201 (7.1)	-2.1 (-3.3, -0.9)
Systemic hypertension (narrow FMQ)	286 (10.1)	358 (12.6)	-2.5 (-4.2, -0.8)
Peripheral oedema (narrow FMQ)	212 (7.5)	337 (11.9)	-4.4 (-5.9, -2.9)

Source: adae.xpt; Software: Python
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
For specific preferred terms under each FMQ, see the table "Adverse Events by FDA Medical Query (Narrow) and Preferred Term…"
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.6. Additional Analyses of Key Adverse Events

Hyperkalemia

As discussed above, there was a higher incidence of AEs, SAEs, and AEs resulting in medication discontinuation related to hyperkalemia[7] in patients on finerenone as compared to placebo, consistent with the mechanism of action of the drug. Most of the AEs related to hyperkalemia were classified as mild in both groups. Two patients on finerenone had SAEs of hyperkalemia and died during the study. Review of the narratives for these patients did not suggest that finerenone played a causative role in these events. Summaries of the narratives for these patients are provided below:

- *Patient* (b) (6): The patient was a 69-year-old Caucasian male who was initially started on finerenone 10 mg daily and was up-titrated to 20 mg daily at Month 1. The patient was diagnosed with stage 4 lung carcinoma of unspecified cell type approximately 10 months after initiation of study drug, which was treated with dexamethasone, morphine, and crizotinib. Study drug was prematurely permanently discontinued approximately one year after the first dose due to a "non-safety related" reason. Two days after finerenone was discontinued, the patient's serum potassium level was 4.7 mmol/L (central laboratory). Seven days after discontinuing study drug, the patient was reported to have the AEs of atrial fibrillation and glomerular filtration rate decreased. Ten days after discontinuing study drug, the patient was found to have a serum potassium level of 7.4 mmol/L on an unscheduled measurement. The patient died 11 days after discontinuing study drug, with the death adjudicated as non-cardiovascular and non-renal. The cause of death was initially thought to be arrhythmia per the investigator; however, "no medical exams confirmed arrhythmia" at the time of death. Approximately two months after the patient's death, "additional information was provided to pharmacovigilance stating lung cancer as additional cause of death."
- *Patient* (b) (6): The patient was a 67-year-old Caucasian female who was initially started on finerenone 10 mg daily and remained on this dose for approximately 1.5 years until premature discontinuation of study drug due to hyperkalemia (potassium value not provided). Study drug was not restarted. Fifteen days after last dose of study drug, the patient was reported to have renal failure, which per the investigator, was due to chemotherapy for active bladder cancer. The patient was not able to be dialyzed. The patient died the same day. The death was adjudicated as non-cardiovascular and non-renal, with the cause of death provided as malignancy.

The proportion of patients with a new incidence of a clinically significant serum potassium elevation (i.e., >6 mmol/L) in FIDELIO-DKD was greater in the finerenone arm (5.8%) compared to the placebo arm (1.9%).

As shown in Table 31, in FIDELIO-DKD, the incidence of hyperkalemia AEs increased in both arms as baseline potassium increased, which is not unexpected. Across the quartiles, the incidence of hyperkalemia in the finerenone arm was approximately 2x greater than in the placebo arm. For the highest quartile (i.e., serum potassium >4.7 mmol/L), the incidence of hyperkalemia AEs was 28.0% for finerenone compared to 15.3% for placebo.

Table 31. Incidence of Hyperkalemia Adverse Events by Baseline Potassium Quartile, Safety Population, Trial 16244

	Finerenone N=2827		Placebo N=2831		
Baseline Potassium	# in Group	n (%) With AE	# in Group	n (%) With AE	Risk Difference (95% CI)
≤4.1 mmol/L	858	94 (11.0)	850	37 (4.4)	6.6 (4.1, 9.1)
>4.1 and ≤4.4 mmol/L	785	132 (16.8)	765	66 (8.6)	8.2 (4.9, 11.5)
>4.4 and ≤4.7 mmol/L	655	142 (21.7)	675	69 (10.2)	11.5 (7.6, 15.4)
>4.7 mmol/L	529	148 (28.0)	541	83 (15.3)	12.6 (7.8, 17.5)

Source: adae.xpt; Software: R
Hyperkalemia includes hyperkalemia and blood potassium increased.
Number in group refers to baseline potassium quartile group.
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; AE, adverse events

The incidence of hyperkalemia AEs is shown in Table 32 by baseline eGFR. Across the subgroups of eGFR, the incidence of hyperkalemia AEs was higher in the finerenone as compared to the placebo arm, with the greatest risk difference observed in patients with a baseline eGFR <60 mL/min/1.73 m^2. In the subgroup with the lowest baseline eGFR (i.e., <25 mL/min/1.73 m^2), 21% of patients in the finerenone arm, as compared to 13% in the placebo arm, had an AE of hyperkalemia.

Table 32. Incidence of Hyperkalemia Adverse Events by Baseline eGFR, Safety Population, Trial 16244

	Finerenone N=2827		Placebo N=2831		
Baseline eGFR (mL/min/1.73 m^2)	# in Group	n (%) With AE	# in Group	n (%) With AE	Risk Difference (95% CI)
<25	66	14 (21.2)	69	9 (13.0)	8.2 (-4.5, 20.8)
25 to <45	1473	325 (22.1)	1499	159 (10.6)	11.5 (8.8, 14.1)
45 to <60	971	143 (14.7)	926	58 (6.3)	8.5 (5.7, 11.2)
≥60	317	34 (10.7)	337	29 (8.6)	2.1 (-2.4, 6.7)

Source: adae.xpt; Software: R
Hyperkalemia includes hyperkalemia and blood potassium increased.
Number in group refers to baseline eGFR group.
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; AE, adverse events

Arrhythmias

Given finerenone's effect on serum potassium levels, analyses were conducted to determine whether finerenone increased the risk of cardiac arrhythmias. As shown in Table 33, the overall incidence of arrhythmia AEs in FIDELIO DKD was lower in the finerenone (3.6%) as compared to placebo (4.5%) arm. Arrhythmia SAEs were uncommon and were reported at a similar incidence in the treatment arms (0.2% in each arm).

Table 33. Adverse Events in the Arrhythmia FMQ (Narrow), Showing Terms Occurring in >0.5% of Patients in Any Arm, Safety Population, Trial 16244

Category of Event Preferred Term	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Any AE	102 (3.6)	127 (4.5)	-0.9 (-1.9, 0.1)
Ventricular extrasystoles	20 (0.7)	21 (0.7)	-0.0 (-0.5, 0.4)
Bradycardia	15 (0.5)	25 (0.9)	-0.4 (-0.8, 0.1)
Atrial fibrillation	12 (0.4)	22 (0.8)	-0.4 (-0.8, 0.0)
Any SAE	7 (0.2)	6 (0.2)	0.0 (-0.2, 0.3)
Any fatal AE	0	0	0 (0, 0)
Any AE leading to discontinuation	0	2 (<0.1)	-0.1 (-0.2, 0.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

Acute Kidney Injury

Given its mechanism of action, finerenone has the potential to cause volume depletion, which can increase the risk of AKI. As such, further analyses were conducted to explore the risk of AKI. The results of the narrow FMQ analysis for AKI are shown in Table 34. The overall incidence of AE's suggestive of AKI was slightly lower in the finerenone arm (4.7%) as compared to the placebo arm (5.1%). Of the preferred terms included in the FMQ, "acute kidney injury" was the most commonly reported preferred term and was reported at a similar incidence in the two arms (4.6% for finerenone versus 4.8% for placebo). All other preferred terms in the narrow AKI FMQ occurred at an incidence of <0.1% in either arm. The incidence of serious AKI events was similar in the two arms (approximately 2%).

Table 34. AKI Treatment-Emergent Adverse Events by AKI FMQ (Narrow) and Preferred Term, Safety Population, Trial 16244

AKI FMQ (Narrow) Preferred Term	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Any AEs	134 (4.7)	144 (5.1)	-0.4 (-1.5, 0.7)
Acute kidney injury	129 (4.6)	136 (4.8)	-0.2 (-1.3, 0.9)
Any serious AEs	57 (2.0)	53 (1.9)	0.1 (-0.6, 0.8)
Acute kidney injury	56 (2.0)	51 (1.8)	0.2 (-0.5, 0.9)
Any fatal AEs	0	1 (0.0)	0.0 (-0.1, 0.1)
Acute kidney injury	0	1 (0.0)	0.0 (-0.1, 0.1)
Any AE with outcome of drug discontinuation	5 (0.2)	9 (0.3)	-0.1 (-0.4, 0.2)
Acute kidney injury	5 (0.2)	7 (0.2)	0.0 (-0.2, 0.2)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs that started or worsened after the first dose of study drug up to 3 days after any temporary or permanent interruption of study drug. Coded as FDA medical query terms.
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AE, adverse event; AKI, acute kidney injury; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in group; n, number of patients meeting criteria; CI, confidence interval

As shown in Table 35, in the majority of patients with an AKI-related AE, the dose of study drug (i.e., finerenone or placebo) was not changed. A similar percentage of patients in both arms had study drug interrupted because of an AKI-related AE (1.4% finerenone versus 1.3% placebo). The incidence of drug withdrawal because of an AKI-related AE was low in both arms (<0.5%).

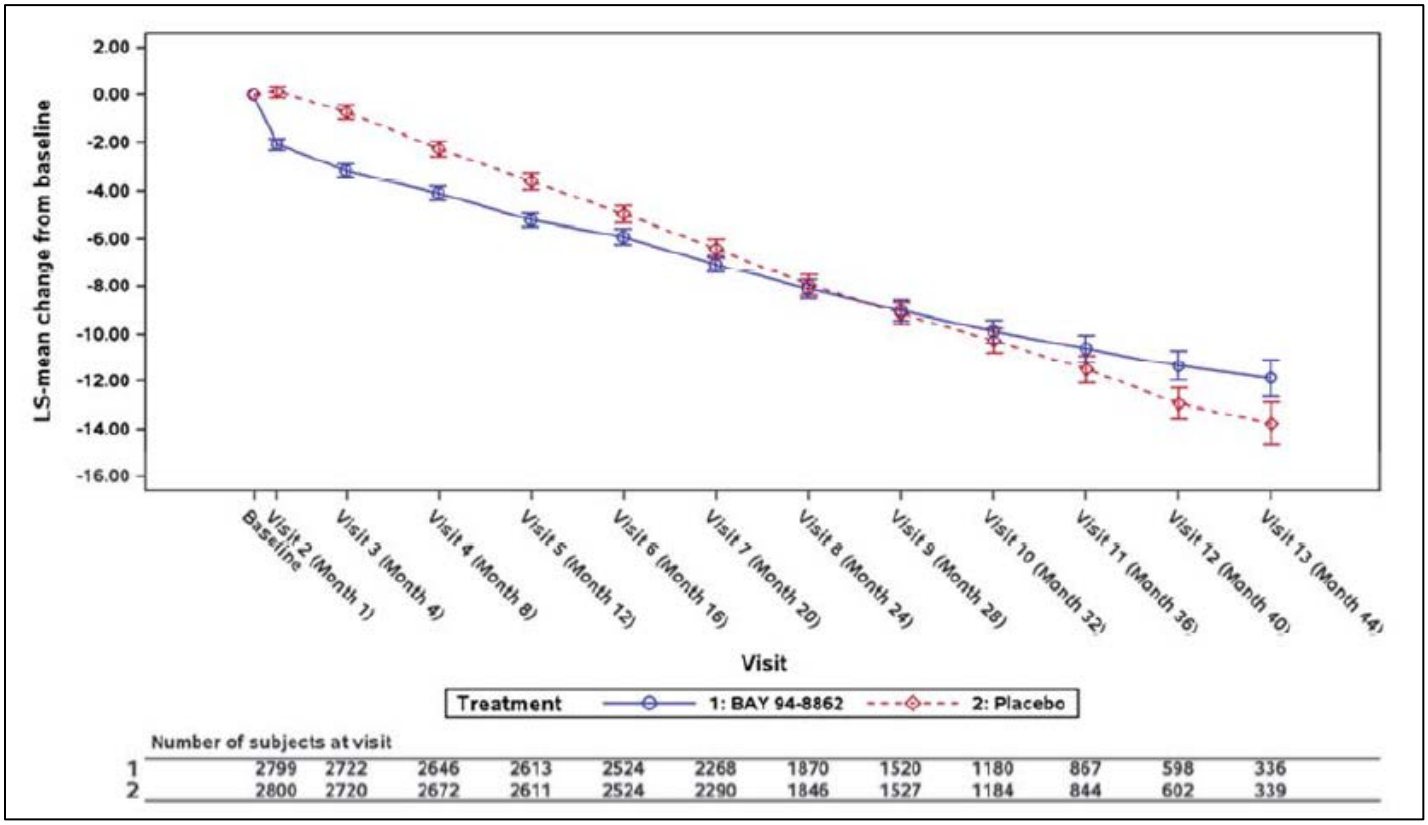
Table 35. Action Taken With Drug Due to Adverse Event in AKI FMQ (Narrow), Safety Population, Trial 16244

Action Taken with Drug	Finerenone N=2827 n (%)	Placebo N=2831 n (%)	Risk Difference (95% CI)[1]
Dose not changed	92 (3.3)	94 (3.3)	0 (-1, 0.9)
Drug interrupted	40 (1.4)	36 (1.3)	0.1 (-0.5, 0.7)
Drug withdrawn	5 (0.2)	9 (0.3)	-0.1 (-0.4, 0.1)
Dose reduced	4 (0.1)	3 (0.1)	0 (-0.1, 0.2)
Not applicable	10 (0.4)	15 (0.5)	-0.1 (-0.5, 0.2)
Unknown	0 (0)	0 (0)	0 (0, 0)

Source: adae.xpt; Software: R
Coded as FDA medical query terms
[1] Risk difference column shows difference (with 95% confidence interval) between total treatment and comparator.
Abbreviations: AKI, acute kidney injury; CI, confidence interval; FMQ, FDA MedDRA Query; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in group; n, number of patients meeting criteria

As shown in Figure 9, initiation of finerenone was associated with an initial decrease in mean eGFR (relative to baseline and the placebo arm). Over time, the mean eGFR decreased in both arms; however, the "chronic slope" (i.e., the rate of decline following the initial drop in eGFR) appeared to be less negative in the finerenone arm than the placebo arm. This pattern is not unexpected for a drug with an acute hemodynamic effect on eGFR that is also effective in slowing the irreversible loss of kidney function in patients with CKD.

Figure 9. Least Square Means of eGFR Absolute Change From Baseline, ITT Population, Trial 16244



Source: Applicant, Clinical Study Report Figure 9-20; verified by FDA
Abbreviations: eGFR, estimated glomerular filtration rate; ITT, intent-to-treat; LS-mean, least squares mean

Hyponatremia

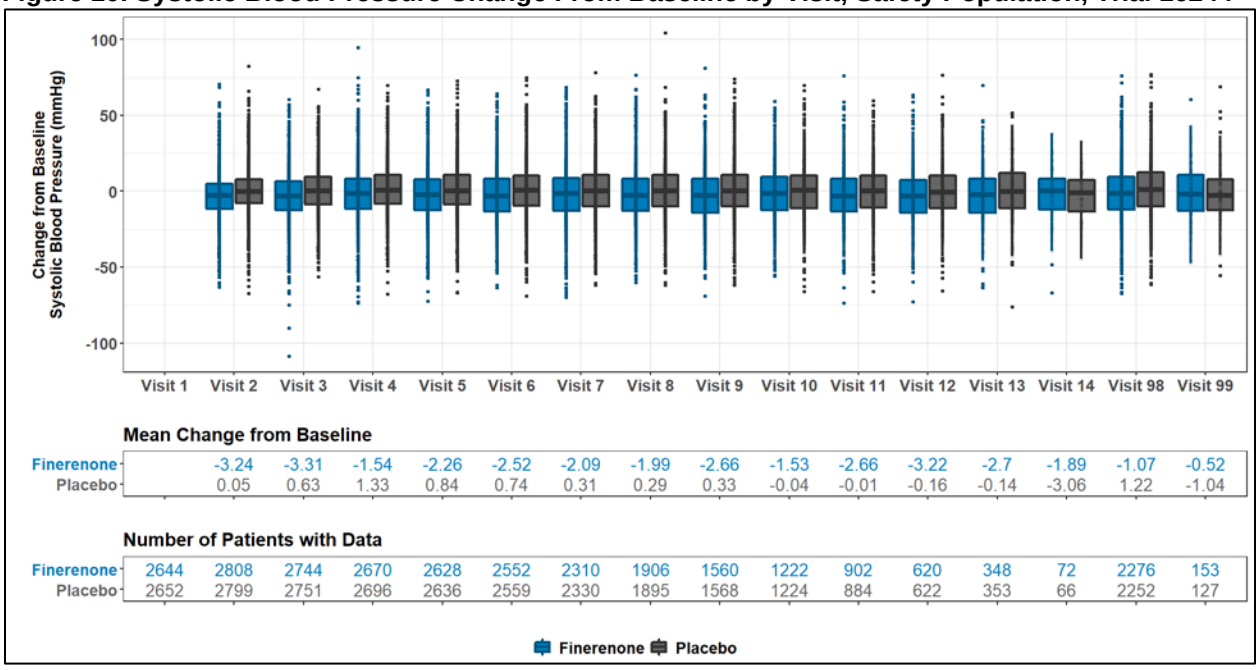
As discussed above, there was a greater incidence of AEs of hyponatremia in the finerenone arm (1.4%) as compared to the placebo arm (0.7%). Most of the TEAEs were classified as mild; SAEs of hyponatremia were uncommon (0.3% finerenone versus 0.04% placebo) and no death was attributed to hyponatremia. One patient (0.04%) in the finerenone arm had his/her medication discontinued for hyponatremia as compared to none in the placebo arm. The proportion of patients with serum sodium levels <135 mmol/L in FIDELIO-DKD was greater in the finerenone (18.3%) as compared to placebo (12.5%) arm, a finding that is expected given the mechanism of action of the drug.

Hypotension

As previously discussed, the incidence of AEs suggestive of hypotension (narrow FMQ) was higher in the finerenone arm (5.3%) as compared to the placebo arm (3.9%) in FIDELIO-DKD; however, SAEs (narrow hypotension FMQ) were uncommon (0.4% finerenone versus 0.2% placebo). The proportion of patients who discontinued study drug due to a hypotension-related AE was low (≤0.3% in both arms).

Changes in systolic blood pressure over time are shown in Figure 10. At the Month 1 visit (Visit 2), mean systolic blood pressure was approximately 3 mmHg lower (from baseline and relative to placebo) in the finerenone arm and remained approximately 2-3 mmHg lower for the duration of the trial. A similar pattern was observed for diastolic blood pressure.

Figure 10. Systolic Blood Pressure Change From Baseline by Visit, Safety Population, Trial 16244



Source: adversusxpt; Software: R
Visit 1 is not shown because for 5656 of 5657 subjects with blood pressure data, visit 1 and baseline are the same day.
Visits 1-4 occurred monthly; study visits occurred every 4 months starting with Visit 5
Visit 98 is end of study combined with premature discontinuation; Visit 99 is post-treatment visit

7.6.1.7. Laboratory Findings

See Section 7.6.1.6 for details regarding laboratory findings for potassium, sodium, and eGFR in FIDELIO-DKD. In FIDELIO-DKD, the proportion of patients with serum magnesium levels <0.62 mmol/L was greater in the finerenone (5.5%) as compared to placebo (4.3%) arm, a finding which is consistent with known effects of other mineralocorticoid receptor antagonists. Analyses of other laboratory data did not reveal any other findings of interest or concern.

7.6.1.8. Vital Signs

See Section 7.6.1.6 for details regarding blood pressure findings in FIDELIO-DKD. Analyses of other vital sign data did not show reveal other findings of interest or concern.

7.7. Key Review Issues Relevant to Evaluation of Risk

There are no issues related to the evaluation of risk that warrant discussion in this section.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Renal Impairment

The PK of finerenone was different in those with renal impairment, which is also the target patient population. A dedicated renal impairment study was conducted where participants with

CL_{CR} >80 mL/min and those with varying severities of renal impairment were given a single 10-mg dose of finerenone (Study 14509).

In those with a CL_{CR} 30 to <50 mL/min and <30 mL/min, the mean residence time was increased, and AUC was increased to 161% and 145% of the AUC in those with a CL_{CR} >80 mL/min. CL/F and Vz/F were decreased. For those with CL_{CR} 50 to 80 mL/min, 30-<50 mL/min, and <30 mL/min, all three PK parameters measured in the urine (AE,ur, %AE,ur, and CL_{CR}) were decreased compared to those with CL_{CR} >80 mL/min. Compared to those with CL_{CR} >80 mL/min, CL_R was 57%, 37%, and 27% in those with CL_{CR} 50 to 80 mL/min, 30-<50 mL/min, and <30 mL/min, respectively. Upon including an outlier in the CL_{CR} 30-<50 mL/min group, the general trend in the data stayed the same, but variability increased. Detailed PK results can be found in Section III.14.2.

AUC of the unbound fraction of finerenone in plasma was increased in those with CL_{CR} 30-<50 mL/min and <30 mL/min to 157% and 147%, respectively, compared to the AUC of the unbound fraction of finerenone in those with CL_{CR} >80 mL/min. The unbound fraction did not change based on renal impairment status. CL/F of the unbound fraction of finerenone decreased in those with CL_{CR} 30-<50 mL/min and <30 mL/min to 64% and 68% of that seen in those with CL_{CR} >80 mL/min, respectively.

Exposure to the inactive metabolites M-1, M-2, and M-3 was increased in renal impairment. In those with a CL_{CR} 50 to 80 mL/min, AUCs increased to 104%, 118%, and 147% for M-1, M-2, and M-3, respectively. In those with a CL_{CR} 30-<50 mL/min AUCs increased to 209%, 178%, and 370% for M-1, M-2, and M-3, respectively. In those with a CL_{CR} <30 mL/min, AUCs increased to 168%, 190%, and 575% for M-1, M-2, and M-3, respectively. C_{max} data were variable between renal impairment groups. The $t_{1/2}$ generally increased with decreasing renal impairment for all metabolites measured.

The LS-mean %-ratio for AUC and C_{max} in those with a CL_{CR} 50 to 80 mL/min, 30-<50 mL/min, and <30 mL/min were compared to those with a CL_{CR} >80 mL/min. The LS-mean %-ratios indicated that those with CL_{CR} 30-<50 mL/min and <30 mL/min had a substantial increase in AUC compared to those with a CL_{CR} >80 mL/min. C_{max} values appear to be elevated for those with a CL_{CR} 30-<50 mL/min; however, this same trend was not seen in those with CL_{CR} <30 mL/min. These results are presented in Table 36.

Table 36. Point Estimators (LS-Means) and 2-Sided 90% CIs for PK Parameters of Finerenone in Plasma After a Single Oral Dose of a 10 mg Immediate Release Tablet*

Ratio	Parameter	Unit	n	CV	Estimated ratio (%)	90% confidence interval (%)
Mild renal impairment / normal renal function	AUC	µg*h/L	8/8	59	101.19	[63.38 ; 161.57]
	AUC_{norm}	kg*h/L	8/8	64	93.69	[56.74 ; 154.72]
	C_{max}	µg/L	8/8	47	109.74	[74.90 ; 160.78]
	$C_{max, norm}$	kg/L	8/8	51	101.60	[67.74 ; 152.39]
Moderate renal impairment normal renal function	AUC	µg*h/L	7/8	59	161.41	[99.45 ; 261.98]
	AUC_{norm}	kg*h/L	7/8	64	158.11	[94.07 ; 265.73]
	C_{max}	µg/L	7/8	47	115.39	[77.70 ; 171.34]
	$C_{max, norm}$	kg/L	7/8	51	113.02	[74.29 ; 171.95]
Severely impaired / normal renal function	AUC	µg*h/L	9/8	59	145.37	[92.26 ; 229.06]
	AUC_{norm}	kg*h/L	9/8	64	144.31	[88.63 ; 234.97]
	C_{max}	µg/L	9/8	47	92.56	[63.86 ; 134.17]
	$C_{max, norm}$	kg/L	9/8	51	91.89	[61.97 ; 136.26]

Source: Applicant, Study 14509, Report PH-36810, Table 2-8.
norm subscript denotes parameter divided by dose per kg body weight
* Excluding an outlier in the moderate renal impairment group
Abbreviations: CI, confidence interval; CV, coefficient of variation; LS-Means, least squares means; PK, pharmacokinetic; AUC, area under the curve

It was determined that dose adjustments are necessary depending on the degree of renal impairment; however, the Applicant is basing this decision primarily on the disease state and not on the increased exposure. A lower eGFR is a risk factor for hyperkalemia in patients with CKD. The lower starting dose for patients with renal impairment in FIDELIO was based on data from the ARTS-DN study that showed patients with an eGFR ≤60 mL/min/1.73m^2 had a mean serum potassium increase by 0.250 mmol/L after 30 days on a 20-mg dose, versus a 0.088 mmol/L potassium increase on a 10-mg dose (Table 37). For those with an eGFR >60 mL/min/1.73m^2, baseline potassium increased by 0.145 and 0.146 mmol/L for the 10 mg/day and 20 mg/day groups, respectively. The greater increase in serum potassium in those with lower eGFR values was the rationale for the reduced dose in those with renal impairment in FIDELIO. The review team agrees to the proposed lower starting dose of 10 mg for patients with eGFR >25 to <60 mL/min/m^2.

Table 37. Change in Serum Potassium (mmol/L) From Baseline to Day 30 in the ARTS-DN Study (Study 16243)

	eGFR ≤60 ml/min/1.73m^2 at Baseline	eGFR >60 ml/min/1.73m^2 at Baseline
Placebo	0.073	-0.002
Finerenone 10 mg QD	0.088	0.145
Finerenone 20 mg QD	0.250	0.146

Source: Applicant calculated data for the ARTS-DN Study.
Abbreviations: eGFR, estimated glomerular filtration rate; QD, once daily

Hepatic Impairment

Finerenone PK was affected in those with hepatic impairment. A dedicated hepatic impairment study was conducted where participants with normal hepatic function, mild hepatic impairment (Child Pugh A), and moderate hepatic impairment (Child Pugh B) were given a single 5-mg dose of finerenone (Study 14510). Results are shown below in Table 38 and show that moderate hepatic impairment increased exposure (AUC) and half-life compared to healthy subjects.

The LS-mean %-ratio for those with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment compared to healthy individuals were 96.4 and 99.1% for C_{max} values, respectively, after a single 5-mg dose. The LS-mean %-ratio for those with mild (Child Pugh A) and moderate (Child Pugh B) hepatic impairment compared to healthy individuals were 108.4 and 138.3% for AUC values, respectively, after a single 5-mg dose.

Table 38. Point Estimates and 90% Confidence Intervals for Ratios of PK Parameters of Total and Unbound Finerenone (N=27)

Parameter	Geo. %CV	Ratio	LS-mean	90% CI
AUC	36.2	CP-A/healthy subjects	1.0838	[0.8169; 1.4379]
		CP-B/healthy subjects	1.3827	[1.0422; 1.8344]
AUC_{norm}	37.2	CP-A/healthy subjects	1.0765	[0.8052; 1.4394]
		CP-B/healthy subjects	1.3354	[0.9988; 1.7855]
C_{max}	36.4	CP-A/healthy subjects	0.9643	[0.7256; 1.2816]
		CP-B/healthy subjects	0.9910	[0.7457; 1.3172]
$C_{max,norm}$	31.0	CP-A/healthy subjects	0.9579	[0.7502; 1.2229]
		CP-B/healthy subjects	0.9572	[0.7497; 1.2221]
AUC_u	36.1	CP-A/healthy subjects	1.0472	[0.7894; 1.3892]
		CP-B/healthy subjects	1.5517	[1.1697; 2.0584]
$C_{max,u}$	40.1	CP-A/healthy subjects	0.9318	[0.6825; 1.2720]
		CP-B/healthy subjects	1.1122	[0.8147; 1.5183]
f_u	11.4	CP-A/healthy subjects	0.9662	[0.8814; 1.0592]
		CP-B/healthy subjects	1.1222	[1.0237; 1.2302]

Source: Applicant, Study 14510, Report PH-3832, Table 2-2.
Abbreviations: AUC, area under the curve; CI, confidence interval; CP, Child Pugh; CV, coefficient of variation; Fu, unbound drug fraction; LS-mean, least squares mean; PK, pharmacokinetic

Pharmacologically inactive metabolites also differed in PK in those with hepatic impairment. M-1 C_{max} values were lower in those with hepatic impairment, with an 18% and 32% reduction in mild and moderate hepatic impairment, respectively. M-1 AUC was similar in hepatic impairment, with a 7% increase in the LS-mean and 11% increase in the LS-mean for mild and moderate hepatic impairment, respectively. M-2 exposure was increased, with the AUC 48% and 77% higher for those with mild and moderate hepatic impairment, respectively. M-3 C_{max} decreased by about 10% in those with mild and moderate hepatic impairment, and AUC increased by about 7% and 26% for those with mild and moderate hepatic impairment, respectively. Mean terminal half-lives were increased for each of the metabolites.

The Applicant did not propose any dose modifications for patients with mild or moderate hepatic impairment. Patients with severe hepatic impairment (Child Pugh C) were not studied, and the Applicant recommends that treatment with finerenone be avoided in this population. PK/PD analyses showed that there was a time-scale separation between the PK of finerenone, which has an elimination half-life of 2 to 3 hours, and the PD response of increased potassium, which has a half-life of several days, with 20 days to get to 99% drug effect. Therefore, if potassium increases were to occur in this population due to an increase in finerenone exposure, it would be quite delayed and immediate risk of hyperkalemia is unlikely. Additionally, pop-PK/PD analyses indicated that the intrinsic effect of finerenone exposure on the risk of hyperkalemia was small; rather, baseline serum potassium is a better indicator of the risk of hyperkalemia during

treatment. Therefore, using the potassium-based titration without dose adjustment seems appropriate for patients with mild or moderate hepatic impairment.

8.2. Drug Interactions

Metabolic Pathway

In vitro metabolism studies demonstrated that both CYP3A4 and CYP2C8 contributed to the metabolism of finerenone. CYP3A4 was primarily responsible for metabolism, accounting for 87 to 89% of metabolic clearance, whereas CYP2C8 was responsible for about 10% of metabolic clearance. Drugs that are inhibitors of CYP3A and CYP2C8 have the potential to increase finerenone exposures and were tested in vivo.

Effect of Other Drugs on Finerenone

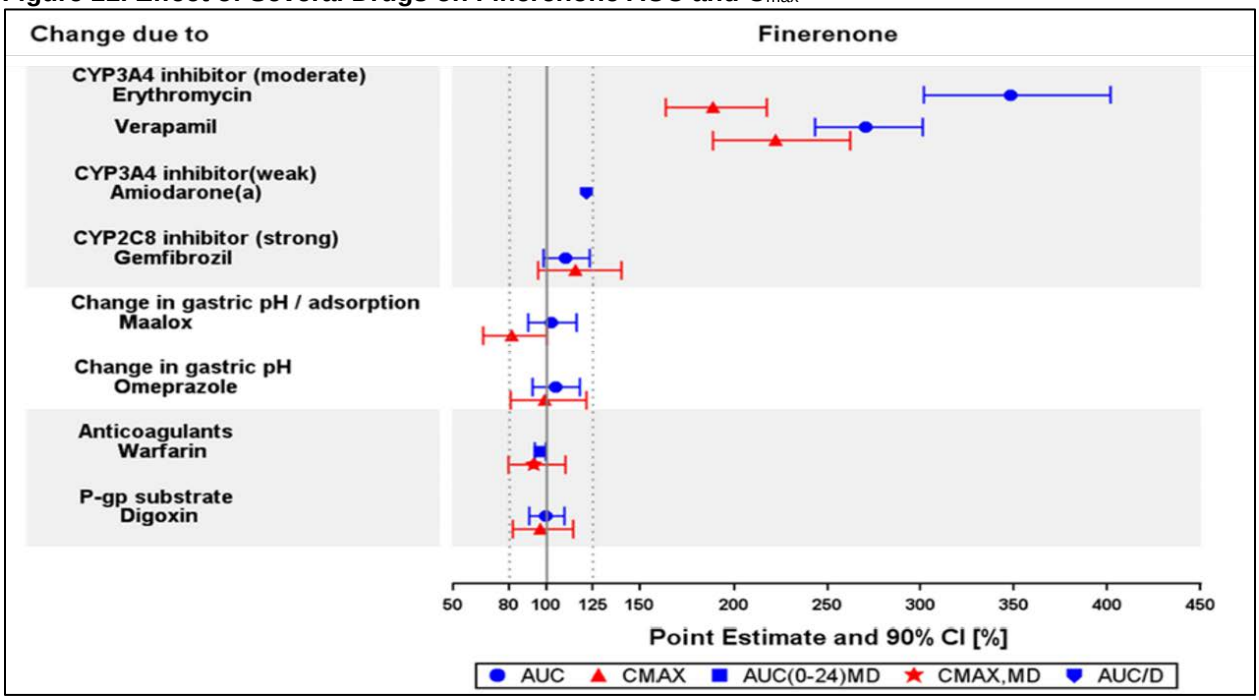
Gemfibrozil, a strong CYP2C8 inhibitor, was dosed to steady state and its effects were evaluated on a single-dose of finerenone. Gemfibrozil increased the AUC of finerenone by 10.1% and the C_{max} by 15.7% (Figure 11). The change in finerenone exposure with a strong CYP2C8 such as gemfibrozil is not clinically significant.

CYP3A inhibitors that were specifically studied include amiodarone, a weak CYP3A inhibitor, erythromycin, a moderate CYP3A inhibitor, and verapamil, another moderate CYP3A inhibitor. The effects of strong CYP3A inhibitors, itraconazole and clarithromycin, and weak inhibitor, fluvoxamine, were also evaluated using PBPK modeling and simulations (Figure 11).

Erythromycin increased finerenone AUC by 248% and C_{max} by 88%. The elimination half-life of finerenone increased from 1.6 to 2.5 hours. Verapamil increased finerenone AUC by 170% and C_{max} by 122%. Interaction with amiodarone was studied in an exploratory popPK analysis of the Phase 2 data. Amiodarone resulted in a 17% lower CL/F and a 21% increase in AUC. Simulations with fluvoxamine administered as 100 mg twice daily showed a 57% increase in AUC and a 38% increase in C_{max}. Simulations with itraconazole administered as 200 mg twice daily showed increases in both finerenone AUC and C_{max} by 531% and 137%, respectively. Simulations with clarithromycin administered as 500 mg twice daily was predicted to increase finerenone AUC and C_{max} by 428% and 125%, respectively. Interactions with CYP3A inhibitors are potentially of clinical significance and are discussed in the next subsection.

The effect of increasing gastric pH was also examined, as finerenone exhibits a decrease in aqueous solubility with increasing pH. Omeprazole had no significant effect on finerenone C_{max} and both omeprazole and Maalox® had no effect on the AUC; however, Maalox® decreased the C_{max} of finerenone by about 19%, likely due to delayed gastric emptying or adsorptive effects in the gastrointestinal tract (Figure 11).

Figure 11. Effect of Several Drugs on Finerenone AUC and C_{max}



Source: Adapted from Applicant's report PH-41449 Figure 14.4/88
[a]Based on popPK analysis 13380 of Study 14563, where use of the weak CYP3A4 inhibitor amiodarone resulted in a 17.4% lower CL/F1 after forward inclusion; however, the inclusion of this covariate effect did not significantly improve model predictions, and was, therefore, not included in the final model.
Abbreviations: AUC, area under the curve; CI, confidence interval

Effect of Finerenone on Other Drugs

In vitro studies indicated that there could be several potential interactions involving transporter systems and CYPs in the context of finerenone as a perpetrator. In vitro, finerenone inhibited P-gp and BCRP with IC_{50} values of 47µM [I_{gut}/IC_{50}: 4.5] and 17µM [I_{gut}/IC_{50}: 12.4], respectively. In a clinical drug interaction study, finerenone had no major effect on digoxin exposures indicating a lack of clinically significant inhibition on P-gp substrates. The I_{gut}/IC_{50} ratio is >10 for BCRP inhibition. While a clinical drug interaction study with a BCRP substrate was not conducted, the risk for clinically significant interaction seems to be low as the C_{max}/Ki ratio for BCRP inhibition is <0.1.

The [I]max,u/IC_{50} values for inhibition towards BSEP, MATE1, MATE2K, OATP1B1/3, OAT1/3, and OCT2 for finerenone, M-1a, M-1b, M-2a, and M-3a, were all below the FDA threshold cutoff for potential drug interactions.

With regard to metabolic interaction, 1+[I]/Ki values for CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 (reversible inhibition), were less than the FDA threshold cutoff of 1.02 for potential drug interactions. For CYP2C8, the basic model showed potential inhibition with a 1+[I]/Ki value above the threshold cutoff; however, the mechanistic static model had a 1+[I]/Ki value of 1.18 which is below the threshold cutoff of 1.25 for potential drug interactions. For CYP3A4 time-dependent inhibition, the 1+[I]/Ki value was 9.29, above the threshold cutoff. 1+[I]/Ki values for all CYP enzymes tested showed there were no potential drug interactions with M-1a, M-1b, M-2a, and M-3a.

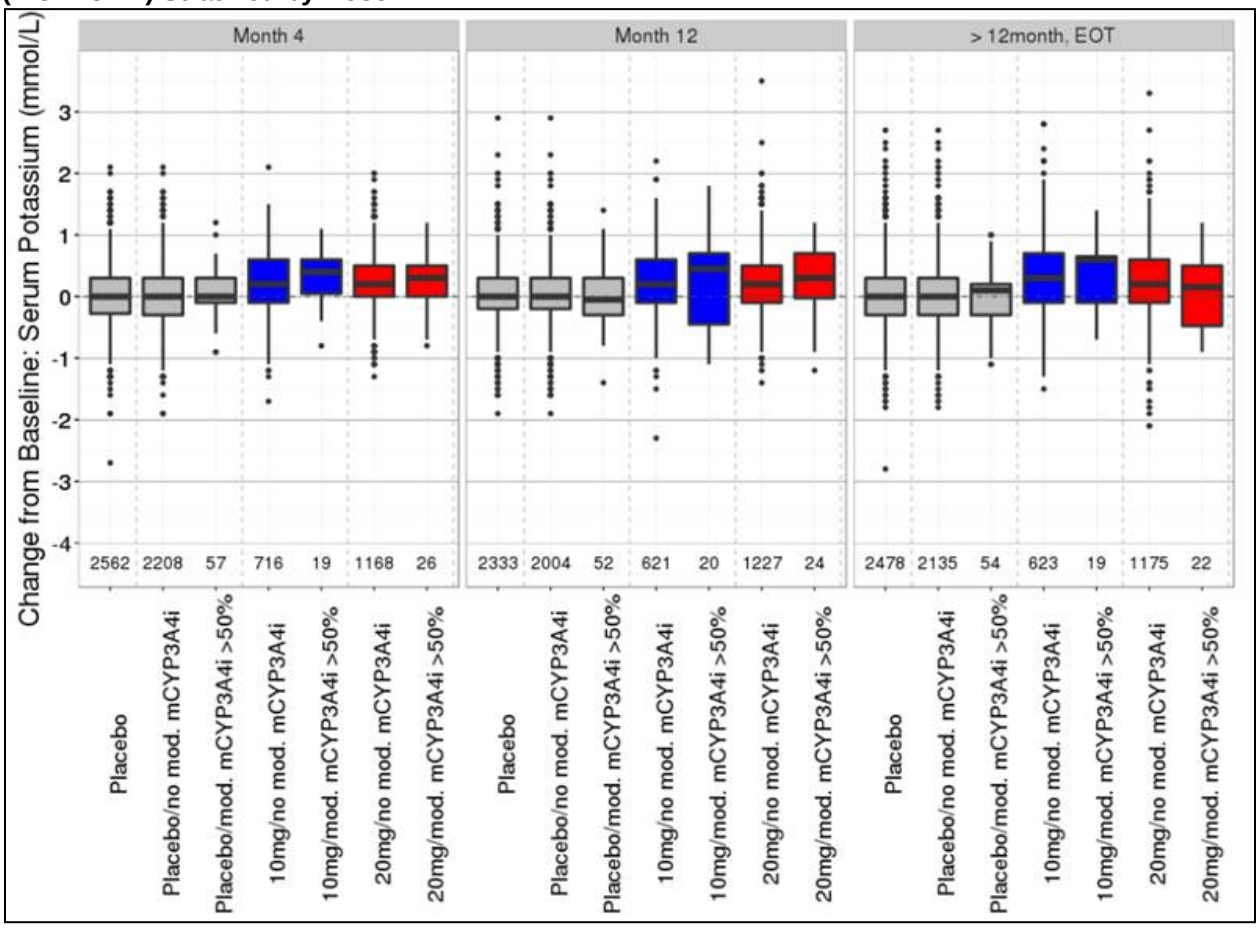
In a phase 1 study, following administration of 20 mg BID finerenone for 10 days, there was modest inhibition of CYP3A4 as reflected by a 21% increase in midazolam AUC. A confirmatory study was conducted with finerenone administered at the highest clinical dose of 20 mg once daily, and the AUC of midazolam increased by 11%. These results suggest that CYP3A4 substrates can be co-administered with finerenone. Repaglinide, a CYP2C8 and OATP1B1 substrate, was administered alone, together with 20 mg of finerenone, or 3 hours after administration of 20 mg of finerenone. AUC of repaglinide increased by 12% when administered with finerenone and 10% when administered 3 hours after finerenone. These results suggest that finerenone does not show clinically significant inhibition of CYP2C8 substrates and also shows lack of inhibition of OATP transport protein. Warfarin was administered after 20 mg finerenone had been administered once daily over 6 days to assess the effect of finerenone on a CYP2C9 substrate. Finerenone had no clinically relevant effect on AUC or C_{max} of R- or S-warfarin.

Dosing Recommendations for Use with CYP3A4 Inhibitors

The Applicant proposes to contraindicate the use of finerenone with strong CYP3A4 inhibitors. While the Applicant did not discuss the rationale for contraindicating the use of strong CYP3A4 inhibitors, the OCP review team agrees with this recommendation for the following reasons – (i) the large increase in exposure to finerenone that is expected with strong CYP3A inhibitors i.e., up to 531% increase in AUC; (ii) uncertainty about safety and in particular the risk of hyperkalemia associated with such a large increase in finerenone exposure; and (iii) lack of available lower strengths to adjust doses appropriately. The clinical development program only tested up to 80 mg administered as a single-dose. There were 23 patients who were on a strong CYP3A inhibitor (possibly due to protocol violations) during the course of FIDELIO DKD (Figure 13); however, this information is not sufficient to support a robust assessment of safety.

Even though moderate and weak CYP3A4 inhibitors resulted in a marked increase in finerenone AUC and C_{max}, the Applicant does not propose any dose adjustment for finerenone with concomitant use of these medications. Figure 12 shows the change in potassium from baseline in patients in the phase 3 study at each finerenone dose with and without moderate CYP3A4 inhibitor use for more than 50% of the time during the studied interval. Within each dosing group i.e., 10 mg or 20 mg, the change in serum potassium was similar with or without concomitant moderate CYP3A4 inhibitor use, which supports the Applicant's approach to not recommend dose-adjustment of finerenone.

Figure 12. Serum Potassium Change From Baseline With and Without Moderate CYP3A4 Inhibitors (mCYP3A4i) Stratified by Dose



Source: Applicant, Report PH-41204, Table 13-94.
The line in the boxplots marks the median. The surrounding box is from the 25th to 75th percentiles. Whisker extensions are defined as 1.5 interquartile range and outliers are shown as points above and below.
Abbreviations: EOT, end of trial

Table 39 compares the % of subjects taking finerenone with a hyperkalemia event to the % of subjects taking placebo with a hyperkalemia event, stratified by concomitant CYP3A4 inhibitor use. Among those treated with finerenone, the proportion of subjects with hyperkalemia events in the weak inhibitor group is slightly numerically greater (relative to the overall population of patients treated with finerenone). In contrast, the proportion is slightly numerically lower in the moderator inhibitor group. Although the sample size for concomitant moderate CYP3A4 is limited, these data do not suggest a dose adjustment is warranted.

Table 39. Hyperkalemia Events Based on Weak or Moderate CYP3A4 Inhibitor Use at Baseline in the FIDELIO-DKD Study (Study 16244)

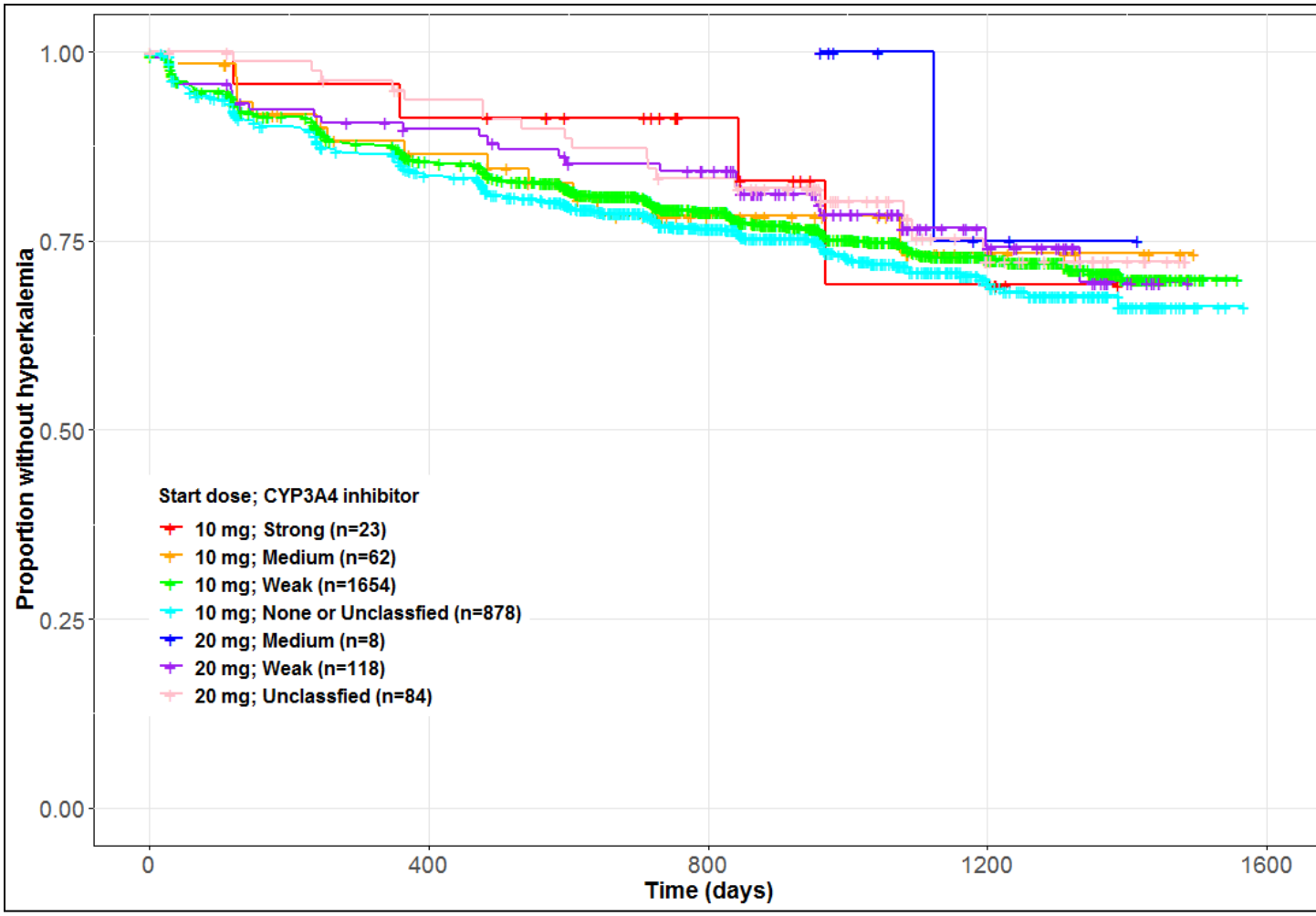
	Finerenone % of subjects with hyperkalemia event*	Placebo % of subjects with hyperkalemia event*
Overall Population	18.3% (516/2827)	9.0% (255/2381)
CYP3A4 Inhibitor		
Weak	19.7% (349/1772)	8.3% (145/1741)
Moderate	15.7% (11/70)	10.7% (6/56)
Unclassified	13.9% (5/36)	8.1% (3/37)
None	15.9% (147/926)	10.4% (101/970)

* Hyperkalemia = hyperkalemia and blood potassium increased

Source: Applicant

Figure 13 shows a Kaplan Meier curve of the incidence of hyperkalemia in patients on finerenone with and without CYP3A4 inhibitors. In those dosed with 10 mg finerenone, patients receiving medium, weak, or no concomitant CYP3A4 inhibitors had a similar incidence of hyperkalemia events over the course of treatment, as demonstrated by the nearly overlapping curves. The number of patients receiving 20 mg finerenone and a moderate CYP3A4 inhibitor is too small to draw meaningful conclusions from the data.

Figure 13. Kaplan Meier Curve Demonstrating Incidence of Hyperkalemia With Concomitant CYP3A4 Inhibitor Use



Source: Pharmacometrics reviewer generated Kaplan Meier curve based on data from the FIDELIO study with subjects from the PK/PD dataset for hyperkalemia. The numbers in this dataset match those presented in Table 39 above and represent patients in the PK/PD dataset for hyperkalemia.

Overall, these results suggest that concomitant use of finerenone with moderate or weak CYP3A4 inhibitors does not contribute significantly to the risk of hyperkalemia. Therefore, concomitant use of finerenone with weak and moderate CYP3A4 inhibitors with dose adjustment as required using the potassium-based titration method proposed in the label seems reasonable.

8.3. Plans for Pediatric Drug Development

Juvenile Rat Studies

Two juvenile rat toxicology studies were conducted. There was no indication of any new target organs of toxicities or greater sensitivity of juvenile animals as compared with adolescent/adult animals. No effects on fertility were observed in juvenile female animals up to the high dose of 10 mg/kg. These data support the conduct of clinical studies in patients down to 6 months of age.

Table 40. Juvenile Toxicity Safety Margins

Study	Nonclinical Data	NOAEL (mg/kg)	Nonclinical exposure (µg•hr/mL)	Safety margins* (multiples)
General Juvenile Toxicology Study in Rat	No mortalities and no dose-limiting toxicities. All effects observed in the adrenal cortex were due to exaggerated pharmacology and thus were not considered adverse.	10	Total: 2390000 Unbound: 1111 (fu =0.0465%)	20X
Reproductive Juvenile Toxicology Study in Rat	No effects on fertility.	10	Total: 2700000 Unbound: 1255	22X

Abbreviations: NOAEL, no observed adverse effect level
*Exposure multiples were based on pharmacokinetics analysis in adults where a 20 mg QD clinical dose resulted in a mean systemic exposure of $AUC_{0\text{-}24hr}$ =686 µg•hr/mL and $AUC_{0\text{-}24hr\text{-}unbound}$ =57 µg•hr/mL (fu =8.33%). The assumption is that the pediatric patients will have the same target AUC. The safety margin calculation was based on unbound AUC.

8.4. Pregnancy and Lactation

A complete battery of developmental and reproductive toxicity studies was conducted. Finerenone did not impair the fertility of male rats. In female rats, signs of impaired fertility were observed starting at 10 mg/kg, which correlated with the histopathology findings in the female reproductive organs indicative of disturbance of the hormonal balance and cyclicity in the 4-week and 13-week studies. In the chronic study, no effects on the female genital tract were observed up to the high dose of 5 mg/kg (about 21 times the exposure at MRHD in terms of AUC unbound). In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day, corresponding to an AUC unbound of 19 times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an AUC unbound of about 25 times that in humans. The doses free of any findings (low dose in rats, high dose in rabbits) provided safety margins of 10 to 13 times for AUC unbound.

Fertility and Early Embryonic Development

Finerenone was tested in a study of fertility and early embryonic development in rats, in which both males and females were treated prior to and during the mating period. Impaired body weight development (either decreased body weight gain or body weight loss) occurred in male and female rats at all dose levels studied (3 to 30 mg/kg/day) in a dose-dependent fashion.

Evaluation of mating and pregnancy data revealed no indication of impairment of male fertility up to the high dose of 30 mg/kg/day. In female animals administered 30 mg/kg, the mean number of corpora lutea was significantly decreased, with decreased implantation sites and increased post-implantation loss, as well as decreased number of viable embryos.

These findings indicate a slight impairment of female fertility as well as early embryonic development at 30 mg/kg; however, these findings are cofounded by maternal toxicity (significant body weight loss or decreased body weight gain) at the same dose level. Summarizing and evaluating all data investigated, the following NOAELs were determined:

- Systemic tolerability: <3 mg/kg/day, based on decreased body weight gain at all dose levels.
- Male fertility: 30 mg/kg/day
- Female fertility and early embryonic development: 3 mg/kg/day

Rat Embryofetal Development

Pregnant female rats were treated with finerenone during organogenesis from GD 6 to GD 17 at doses of 0, 3, 10 and 30 mg/kg/day. Finerenone resulted in maternal toxicity demonstrated by significantly reduced body weight gain starting at 10 mg/kg/day, with approximately 50% reduced body weight gain at 30 mg/kg/day. The mean placental weight and mean fetal weight were also reduced starting at 10 mg/kg/day.

The highest numbers of malformations or variations on a fetal basis were found in the high-dose group, although the numbers were generally within the historical control range. The incidence of skeletal variations was increased starting at 10 mg/kg/day and consisted of retarded ossification (calcaneus, some cervical vertebral bodies, some phalanges), coinciding with signs of maternal toxicity and reduced fetal weight at ≥10 mg/kg. The extent of affected bones was also increased at the high dose. One fetus in the high dose (30 mg/kg) group (1 out of 240 fetuses in this group) showed a complex malformation of the heart and major vessels and a single rare malformation (double aortic arch) which was not seen in historical controls. These findings are disclosed in the label. A double aortic arch was also observed in one fetus in the high dose group (100 mg/kg) in the pilot rat embryofetal development study. Summarizing and evaluating all data investigated the following NOAELs were determined:

- Maternal toxicity: 3 mg/kg/day (based on decreased body weight gain at ≥10 mg/kg/day).
- Developmental toxicity: 3 mg/kg/day (based on decreased fetal body weight ≥10 mg/kg/day and skeletal malformations at 30 mg/kg/day).

Rabbit Embryofetal Development

Pregnant female rabbits were treated with finerenone during organogenesis from GD 6 to GD 20 at doses of 0, 0.25, 0.75 and 2.5 mg/kg/day.

Finerenone was well tolerated at the dose levels of 0.25 and 0.75 mg/kg/day. At the high dose of 2.5 mg/kg/day, there were signs of maternal toxicity, demonstrated by reduced body weight gain or even body weight loss and reduced food intake mainly in the first week of dosing. There were no effects on external, visceral, and skeletal variations and no signs of an increase in malformations were found at any dose levels.

Summarizing and evaluating all data investigated the following NOAELs were determined:

- Maternal toxicity: 0.75 mg/kg/day (based on decreased body weight gain at 2.5 mg/kg/day).
- Developmental toxicity: 2.5 mg/kg/day.

Pre- and Postnatal Development Study

Pregnant female rats were dosed with finerenone from GD 6 to Lactation Day (LD) 21 with doses of 0, 1, 3 and 10 mg/kg/day. Finerenone was generally tolerated in F0 dams, with some effects on body weight and food consumption at 10 mg/kg/day. Adverse effects, including lower birth weight, an increase in locomotor activity and postnatal mortality, were evident for the subsequent progeny following doses of ≥3 mg/kg/day. Drug concentration in the maternal milk was not measured, but toxicokinetic analysis in F1 pups showed that the mean concentration of finerenone in the pups on PND 7 was between 17 and 24% of the C_{max} value in the dams and increased roughly proportionally with increase of maternal dose. Considering the relatively short half-life of finerenone (7-9 hours in rats with oral administration), the data suggest that the finerenone detected in the F1 pup plasma came from the milk and not from trans-placenta exposure during the pregnancy.

Based on the findings in this study, the NOAEL is considered to be 3 mg/kg/day for dams. Due to postnatal deaths, the NOAEL for the F1 generation into adulthood is considered to be 1 mg/kg/day.

Summary of Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

A summary of the nonclinical data supporting labeling on Fertility, Pregnancy and Lactation is provided in Table 41 A summary of reproductive toxicity safety margins is provided in Table 42 See Section 13.1.4.2 Reproductive Toxicology for detailed information on these studies.

Table 41. Nonclinical Data Supporting Labeling on Fertility, Pregnancy and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In the embryo-fetal toxicity study in rats, finerenone resulted in reduced placental weights and signs of fetal toxicity, including reduced fetal weights and retarded ossification at the maternal toxic dose of 10 mg/kg/day corresponding to an (b) (4) ($AUC_{unbound}$) (b) (4) times that in humans. At 30 mg/kg/day, the incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch) at an (b) (4) of about 25 times that in humans.
	(b) (4)
	When rats were exposed during pregnancy and lactation in the pre- and postnatal developmental toxicity study, increased pup mortality and other adverse effects (lower pup weight, delayed pinna unfolding) were observed at about 4 times the AUC unbound expected in humans. In addition, the offspring showed slightly increased locomotor activity, but no other neurobehavioral changes starting at about 4 times the AUC unbound expected in humans. The

Labeling Section	Nonclinical Data
	dose free of findings provided a safety margin of about 2 for AUC unbound. (b) (4) (b) (4)
8.2 Lactation	
8.3 Females and Males of Reproductive Potential	See Section 8.1, 8.2 and 13.1.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	(b) (4)

Source: generated by the pharmacology/toxicology reviewer
Abbreviations: AUC, area under the curve

Table 42. Reproductive Toxicity Safety Margins

		Nonclinical Exposure		
Study	NOAEL (mg/kg)	Total AUC (µg•hr/L)	Unbound AUC (µg•hr/L)	Safety Margins* (Multiples)
Fertility rat (male)	30	1842506	857	15
Fertility rat (female)	3	1190202	553	10
EFD rat	3	1220000	567	10
EFD rabbit	2.5	395000	711	12
PPND rat	1	214000	100	2

Source: pharmacology/toxicology reviewer's table.
* Exposure multiples were based on population pharmacokinetics analysis where a 20 mg QD clinical dose resulted in a mean systemic exposure of $AUC_{0\text{-}24hr}$ =686 µg•hr/L and AUC 0-24hr unbound =57 µg•hr/mL (fu =8.33%). The free fractions (fu) is 0.0465% in rat plasma and 0.18% in rabbit plasma. The safety margin calculation was based on unbound AUC.
Abbreviations: AUC, area under the curve; EFD, embryo-fetal development; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development

Discussion and Conclusions of Human Data and Labeling

Pregnancy

There are no data on the use of finerenone in human pregnancy. In embryo-fetal development studies in pregnant rats and rabbits, no adverse effects were observed on fetal growth or development at 10 and 12 times the human dose (by AUC), respectively. Therefore, there is no requirement for embryofetal toxicity language in Warnings and Precautions.

Lactation

There are no data on the presence of finerenone in human milk, the effects of the drug on the breastfed infant, or on milk production. Finerenone is likely present in rat milk. When a drug is present in rat milk, it is likely to be present in human milk.

Adverse effects, including increased pup mortality, were observed in rats during the pre- and postnatal developmental toxicity study at about 4 times the $AUC_{unbound}$ expected in humans. Because drug concentration in animal milk does not directly correlate to drug concentration in human milk, we cannot establish the NOAEL dose in humans based on animal findings. Since the drug will likely be present in human milk and since there were reports of pup mortality in rats exposed to finerenone during lactation, breastfeeding is not recommended during treatment with

finerenone. This recommendation will appear under Highlights, Use in Specific Populations 8.2, and Patient Counseling Information.

Females and Males of Reproductive Potential
There are no reports of finerenone adversely effecting human fertility. Based on animal studies, finerenone has no effect on male fertility. Finerenone impairs female fertility at 20 times AUC to the maximum human exposure. These data will be presented under subsection 13.1. There are no data to suggest finerenone interacts with systemic hormonal contraceptive.

Additionally, in animal reproduction studies, finerenone administered in pregnancy did not result in embryotoxicity or structural malformation at 10-13X for $AUC_{unbound}$. Therefore, subsection 8.3 will be omitted.

9. Product Quality

The Office of Pharmaceutical Quality Review team has assessed NDA 215341 with respect to Chemistry, Manufacturing, and Controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such OPQ recommends approval of this NDA from a quality perspective.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure

The Applicant has adequately disclosed financial arrangements with clinical investigators and FIDELIO-DKD appears to have been conducted in compliance with U.S. regulations pertaining to Good Clinical Practice. No clinical sites were inspected because review of financial disclosure information did not raise concern, primary efficacy findings were not driven by a single site, and each site contributed a relatively small proportion of patients to the study.

11. Advisory Committee Summary

The application does not raise significant or controversial issues regarding the safety or effectiveness of the drug that would merit outside expertise or public discussion; therefore, no Advisory Committee Meeting was held for this application.

III. Appendices

12. Summary of Regulatory History

The original IND was received on May 15, 2013. FDA granted Fast-Track designation on February 4, 2015. An End-of-Phase 2 meeting was held on April 27, 2015. A pre-NDA meeting was held on September 8, 2020. At the meeting, the sponsor presented topline results for the FIDELIO-DKD study. It was noted that the trial met its primary endpoint with directional consistency amongst the components, although there were few renal deaths. The trial met its key secondary cardiovascular composite endpoint, with directional consistency amongst the components, except for the incidence of non-fatal stroke which was similar in both treatment arms. The NDA was granted priority review designation on December 18, 2020.

13. Pharmacology Toxicology: Additional Information and Assessment

13.1. Summary Review of Studies Submitted Under the IND

13.1.1. Primary Pharmacology and Mechanism of Action

Table 43. Primary Pharmacology Studies

Study	Findings
Functional cellular transactivation assay	Antagonizes human mineralocorticoid receptor with an IC_{50} of 17nM
Stroke-prone spontaneous hypertensive rat model	Protected from both heart and kidney damages and improved survival at 10 mg/kg in this model.
DOCA-salt challenged rat model	Prevented functional as well as structural damages in the heart and kidney in this hypertension model, at doses (≤1 mg/kg) that did not reduce arterial blood pressure.
Secondary pharmacology	Exhibited no activity at any other steroid hormone receptor and on 65 receptors and ion channels at 10µM

Source: Pharmacology/toxicology reviewer's table
Abbreviations: DOCA, deoxycorticosterone acetate

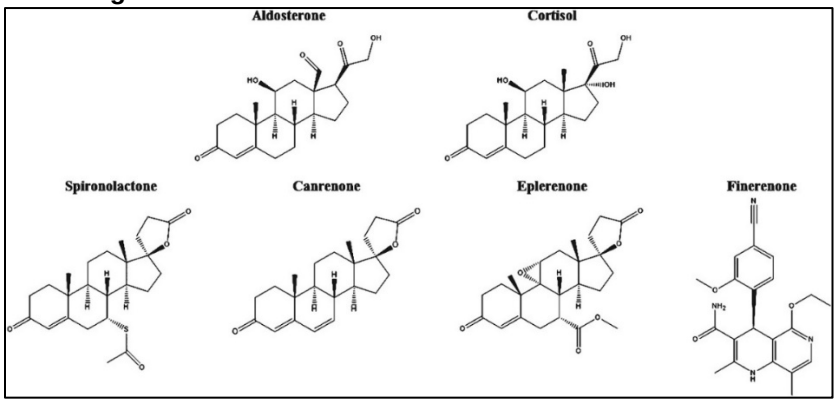
This new molecular entity developed by Bayer is the first aldosterone antagonist that is not steroidal in structure. This non-steroidal structure confers a distinct pharmacodynamic as well as clinical profile. The Applicant proposed that finerenone be established as the first in a new class called non-steroidal mineralocorticoid receptor antagonist. The data supporting this request is outlined in three arguments below:

Chemical Structure

- The EPC for spironolactone and eplerenone, the two approved drugs with similar mechanism of action, is aldosterone antagonist.
- Structurally, spironolactone and eplerenone bear the typical steroidal ring structure (four linked carbon rings) as the natural mineralocorticoid receptor (MR)

ligands aldosterone and cortisol. But finerenone has a non-steroidal, dihydropyridine-based structure (Figure 14).

Figure 14. Molecular Structures of Natural Mineralocorticoid Receptor (MR) Ligands and Synthetic MR Antagonists



Source: (Bramlage et al. 2016)

Pharmacology

- The non-steroidal structure of finerenone confers a different pharmacodynamic profile in comparison to the steroidal MR antagonists. Finerenone has greater MR selectivity than spironolactone and higher receptor affinity than eplerenone in vitro (Table 44) and more potently blocks MR independent of the agonist (i.e., aldosterone or cortisol).

Table 44. In Vitro Receptor Profiles of Spironolactone, Eplerenone and Finerenone

	Spironolactone	Eplerenone	Finerenone
Mineralocorticoid receptor IC_{50} (nM)	24.2	990	17.8
Glucocorticoid receptor IC_{50} (nM)	2410	≥21 980	≥10 000
Androgen receptor IC_{50} (nM)	77.1	≥21 240	≥10 000
Progesterone receptor IC_{50}/EC^{a}_{50} (nM)	740[a]	≥31 210	≥10 000
Oestrogen receptor α IC_{50} (nM)	5970	≥30 000	≥10 000
Oestrogen receptor β IC_{50} (nM)	4940	≥30 000	≥10 000

In vitro potency and selectivity of spironolactone, eplerenone, and finerenone in functional cell-based steroid hormone receptor transactivation assays. (Adapted from Pitt et al. 2012).

[a] Spironolactone is an agonist of the progesterone receptor and the respective EC50 value is therefore given.

Source: Applicant's table

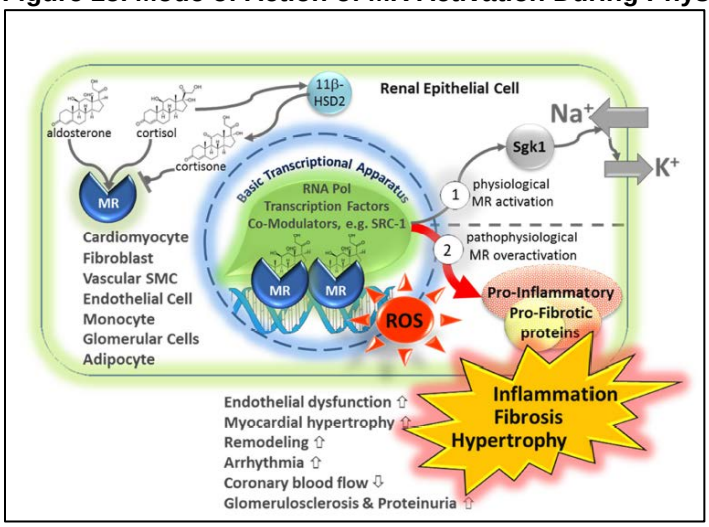
Compared with the first-generation spironolactone, finerenone displays much higher selectivity for MR over other steroid hormone receptors, suggesting that clinical use of finerenone should be associated with much less off-target adverse events like gynecomastia and impotence in men or menstrual irregularities in pre-menopausal women. Compared with the second-generation eplerenone, finerenone targets the MR with a higher affinity.

The drug target for all drugs in this class is mineralocorticoid receptor (MR). MR is mainly expressed in renal cells (tubular epithelia, glomerular), but also in vascular smooth muscle cells,

endothelial cells, fibroblasts, cardiomyocytes, adipocytes, and immune cells like macrophages. MR has high affinity for both aldosterone and cortisol in humans. But the majority of aldosterone-responsive cells express the enzyme 11-beta-hydroxysteroid dehydrogenase, which has no effect on aldosterone, but converts cortisol to cortisone. Cortisone has only a very weak affinity for MR, allowing aldosterone to bind its receptor without competition.

The MR belongs to the superfamily of nuclear hormone receptors, upon ligand (aldosterone or cortisol) binding, it translocates from the cytosol to the nucleus, where it binds to regulatory regions of target genes. Under physiological conditions, MR enables sodium retention and potassium efflux through transcriptional and phosphorylation pathways. Under conditions of elevated aldosterone release, MR overactivation could cause expression of pro-inflammatory and fibrotic proteins that lead to fibrosis in the cardiomyocytes, glomerular cells and other cell types that can cause organ damage in patients with heart failure, hypertension and chronic kidney disease (see Figure 15).

Figure 15. Mode of Action of MR Activation During Physiological and Pathophysiological States



Source: Applicant's figure
Abbreviations: MR, mineralocorticoid receptor; ROS, reactive oxygen species; SMC, smooth muscle cell

Preclinical studies demonstrate that there is a greater reduction in cardiovascular end-organ damage, fibrosis and proteinuria with finerenone compared with equi-natriuretic doses of eplerenone (Kolkhof et al. 2014). These findings are supported by the finding that finerenone exhibits dose-dependent anti-inflammatory and anti-fibrotic effects at doses that do not affect systemic blood pressure. By contrast, eplerenone reduced markers of inflammation and fibrosis only at doses that significantly reduced blood pressure. These preclinical findings stimulated the hypothesis that use of finerenone is associated with a more pronounced anti-inflammatory and anti-fibrotic effect combined with a reduced risk of developing hyperkalemia (Naegele et al. 2016). This suggests that finerenone has a more favorable balance of anti-hypertrophic/anti-fibrotic effects versus renal electrolyte effects (natriuresis and potassium retention) in comparison to steroidal MRAs. This could alleviate the risk of developing hyperkalemia and kidney dysfunction, which has limited the use of steroidal MRAs particularly when given on top of standard of care therapy such as ACEIs or ARBs that also cause hyperkalemia, particularly in patients with preexisting kidney dysfunction.

Clinical Indications and Safety

Spironolactone is approved for primary hyperaldosteronism, hypertension and heart failure and eplerenone is approved for hypertension. Finerenone is indicated (b) (4) (b) (4) to reduce the risk of (b) (4) cardiovascular (b) (4) in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Finerenone does not lower arterial blood pressure at doses that slow the progression of CKD in T2D.

Clinical data available to date also support that the structural and pharmacological differences between finerenone and steroidal MRAs have clinical relevance in reducing adverse events such as hyperkalemia and sexual side-effects.

The completed clinical trials with finerenone for CKD in T2D have established the efficacy and safety of finerenone in these patients, with the recent FIDELIO-DKD study demonstrating statistically and clinically significant reductions in CKD progression as well as the risk of major cardiovascular events. All patients randomized in FIDELIO were treated with maximally tolerated labeled dose of ACEi or ARB with manageable risk of hyperkalemia, thus demonstrating a favorable benefit-risk profile in patients at high risk for CKD progression, CV events and hyperkalemia. Importantly, most hyperkalemia events in FIDELIO were mild or moderate with a low rate of treatment discontinuation and no fatal hyperkalemia events. Consistent with the selectivity profile of finerenone for MR, no gynecomastia or sexual side-effects have been reported in the large development program.

Conclusion and Recommendation

Taken together, finerenone possesses a distinct structural, pharmacological and clinical profile that does not fit into the existing EPC (aldosterone antagonist) created for spironolactone and eplerenone. The proposed new EPC (nonsteroidal mineralocorticoid receptor antagonist) is scientifically valid and supported by the submitted in vitro and animal data. This new EPC also seems to be clinically meaningful as it conveys a differentiating property of finerenone that could help the prescribing physicians to understand the basis of the drug product's clinical safety profile.

The reviewing pharmacologist recommends that a new EPC (nonsteroidal mineralocorticoid receptor antagonist) be created for finerenone.

13.1.2. Safety Pharmacology

Table 45. Safety Pharmacology Studies

Study	Findings
In vitro hERG study of BAY 94-8862	The parent compound (BAY 94-8862) as well as three main human metabolites of BAY 94-8862, i.e., BAY 1117267, BAY 1117268, and BAY 1117271, did not interfere with cardiac repolarization in vitro (hERG K+ current).
CV safety pharmacology Species: Dog NOEL: 10 mg/kg	The PQ interval (dog) was slightly shortened at doses higher than 10 mg/kg. No adverse effects were seen with regard to hemodynamic and other ECG parameters.
CNS safety pharmacology studies Species/strain: Wistar rat NOEL: 30 mg/kg	No effects
Respiratory safety pharmacology Species/strain: Wistar rat NOEL: 30 mg/kg	No effects

Source: Pharmacology/toxicology reviewer's table
Abbreviations: CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; NOEL, no observable effect level; hERG, human ether-a-go-go-related gene

13.1.3. ADME/PK

Table 46. In Vitro Plasma Protein Binding Across Species

Species	Concentration [µg/L]	f_u [%][a]	C_b/C_p
CD-1 mouse (m)	440 to 3150	0.0772	
	66500	0.120	
Wistar rat (m)	515 to 5270	0.0465	0.549
	100000	0.0682	0.601
Cynomolgus monkey (f)	95.5 to 4396	2.55	
	85069	4.20	
Beagle dog (f)	99.0 to 4393	5.49	0.723
	83087	6.09	0.779
Man (m)	94.5 to 4288	8.33	0.935
	87549	12.6	1.09
Albumin	5287	16.4	
α-1 Acidic glycoprotein	4934	59.3	
α-Globulins	4988	58.9	
γ-Globulins	4948	84.4	
LDL	4984	59.8	
William's Medium (incl. 10% FCS)	105	56.2	
William's Medium (incl. 10% FCS)	10420	60.4	

a = fraction of free (unbound) drug in plasma

Source: Applicant's table
Abbreviations: FCS, fetal calf serum; LDL, low density lipoprotein; Fu, unbound drug fraction

The data in Table 46 indicate the vast difference between in vitro plasma protein binding in humans compared with the species used in the animal toxicology studies, especially the Wistar rat, which was used in the chronic toxicology study and 3 of 4 reproductive toxicology studies. Thus, it is important to base safety margins on unbound AUCs (reflective of the exposure of the free drug that can bind to the mineralocorticoid receptor in plasma) rather than total exposure in the plasma.

Table 47. Toxicokinetic Data From Pivotal Nonclinical Studies

Study	Major Findings
General Toxicology Studies	
26-week rat study Sample collection times: steady state Accumulation: considerable accumulation after multiple dose, especially in females (2.6- to 6.0-fold in females; 1.4- to 3.4-fold in males) Dose Proportionality: approximately dose proportional NOAEL (mg/kg): 5 (M); 1.5 (F) Safety margin: 6X (M); 8X (F)	**Summary of TK Parameters of Finerenone at Steady State (on Day 164) in the 26-Week Rat Study** Source: Applicant's table
39-week dog study Sample collection times: steady state Accumulation: AUC was moderately higher after repeated dosing Dose proportionality: AUC more than dose proportional NOAEL: 0.5 mg/kg/day Safety margin: 2X	**Summary of TK Parameters of Finerenone at Steady State (on Week 39) in the 39-Week Dog Study (Males and Females Pooled)** Source: Applicant's table
Reproductive Toxicology Studies	
Rat EFD study Developmental NOAEL: 3 mg/kg/day Safety margin: 10X	**Summary of TK Parameters of Finerenone in Female Rats at GD17 After Daily Oral Administration From GD 6 to GD 17.** Source: Applicant's table

Sex		Male			Female		
Dose	[mg/kg]	1.5	5	15	0.5	1.5	5
AUC (0-24)	[µg·h/L]	118000	704000	1980000	349000	992000	1990000
$AUC_{(0-24)norm}$	[kg·h/L]	78.5	141	132	699	661	398
C_{max}	[µg/L]	7610	42500	107000	17000	46500	101000
$C_{max\ norm}$	[kg/L]	5.07	8.50	7.12	33.9	31.0	20.2
$C(24)/C_{max}$	[%]	35.2	32.2	48.7	73.2	80.7	74.2
RA-AUC(0-24)	[%]	137.2	337.1	197.5	601.0	332.0	351.9
RA- C_{max}	[%]	185.9	241.6	211.1	525.1	257.5	311.4

Dose	[mg/kg/day]	0.5	1.5	5
AUC(0-24)	[µg·h/L]	2110[a]	9910	59500
$AUC_{(0-24)norm}$	[kg·h/L]	4.22[a]	6.61	11.9
C_{max}	[µg/L]	560	2180	8350
$C_{max,norm}$	[kg/L]	1.12	1.45	1.67
$C_{(24)}/C_{max}$	[%]	0.1	0.2	1.9
t_{max}	[h]	0.771	0.841	1.09
R_AAUC	[%]	137	170	199
R_AC_{max}	[%]	108	105	123

Female, Day 17

Dose	[mg/kg]	3		10		30	
equiv. Dose	[mg/kg]	3		10		30	
Time [h]		gMean [µg/L]	gSD	gMean [µg/L]	gSD	gMean [µg/L]	gSD
1		54400	1.07	99100	1.11	145000	1.08
4		58200	1.03	110000	1.14	142000	1.08
7		57100	1.08	106000	1.10	148000	1.13
24		43600	1.15	73100	1.08	96500	1.22

Parameter	Unit						
AUC(0-tlast)	µg·h/L	1220000	1.06	2200000	1.08	2990000	1.13
AUC(0-tlast)norm	kg·h/L	407	1.06	220	1.08	99.7	1.13
tlast	h	24.0	1.00	24.0	1.00	24.0	1.00
Cmax	µg/L	59200	1.06	113000	1.12	153000	1.11
Cmax,norm	kg/L	19.7	1.06	11.3	1.12	5.09	1.11
tmax	h	3.39	2.06	3.79	2.22	4.24	2.32
C(tint)/Cmax	%	73.6	1.18	64.6	1.12	63.2	1.16
t(int)	h	24.0	1.00	24.0	1.00	24.0	1.00

Study	Major Findings
Rabbit EFD study Developmental NOAEL: 2.5 mg/kg/day Safety margin: 12X	**Summary of TK Parameters of Finerenone in Female Rabbits at GD 20 After Daily Oral Administration From GD 6 to GD 20 (n=3).**

BAY 94-8862

Dose	[mg/kg]	0.25		0.75		2.5	
		gMean [µg/L]	gSD	gMean [µg/L]	gSD	gMean [µg/L]	gSD
Parameter	Unit						
AUC(0-24)	µg·h/L	60500	1.24	145000	1.11	395000	1.13
AUC(0-24)norm	kg·h/L	242	1.24	194	1.11	158	1.13
Cmax	µg/L	4730	1.04	9370	1.17	28900	1.11
Cmax,norm	kg/L	18.9	1.04	12.5	1.17	11.6	1.11
tmax*	h	1.00		1.00		2.00	
C(24)/Cmax	%	31.6	1.45	40.3	1.07	32.5	1.06
RA-AUC(0-24)	%	173	1.19	141	1.20	125	1.06
RA-Cmax	%	210.5	1.06	146.5	1.21	137.9	1.03

* = median
RA-C_{max} = ratio of C_{max} from Day 20 to Day 6
RA-AUC(0-24) = ratio of AUC(0-24) from Day 20 to Day 6

Source: Applicant's table

Abbreviations: AUC, area under the curve; EFD, embryo-fetal development; GD, gestation day; NOAEL, no observable adverse effect level; TK, toxicokinetic

The safety margin calculation is based on data from population pharmacokinetics, at 20 mg/day (MRHD), total AUC was 686 µg·hr/L, unbound AUC was 57 µg·hr/L.

13.1.4. Toxicology

13.1.4.1. General Toxicology

Study Number/ Title: Repeated Dose Systemic Toxicity Study in Wistar Rats (6-Months Daily Administration by Oral Gavage)

Key Study Finding

- Exaggerated pharmacological effects on histology of the adrenal cortex (Z. glomerulosa mainly).

Table 48. Study Information for Repeated Dose Systemic Toxicity Study in Wistar Rats

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 0.5, 1.5 and 5 mg/kg/day (females) 0, 1.5, 5 and 15 mg/kg/day (males)
Route of administration:	Oral Gavage
Formulation/vehicle:	Ethanol/Solutol HS15®/Tap water (10/40/50; v/v/v)
Species/strain:	Wistar Rat
Number/sex/group:	20/sex/group
Age:	7 weeks
Satellite groups/unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Abbreviations: GLP, good laboratory practice

Table 49. Observations and Results for Repeated Dose Systemic Toxicity Study in Wistar Rats

Parameters	Major Findings
Mortality	One female died at the high dose (no cause identified)
Clinical signs	Piloerection in females at highest dose (2/20)
Body weights	At the high dose (15 mg/kg in males, 5 mg/kg females) body weight development was marginally reduced. At the end of the treatment period, the animals in the high dose group showed a body weight reduction of 6.4% and 4.2%, in males and in females, respectively.
Ophthalmoscopy	No effect
ECG	Not recorded
Hematology	Slight decrease in erythrocyte count (5 to 6%) in males at the high dose of 15 mg/kg and starting after 3 months treatment also at 5 mg/kg. Hemoglobin concentration was decreased starting after 3 months treatment in females treated at the high dose of 5 mg/kg. MCH and MCHC (except day 87) value was slightly increased at the high dose of 15 mg/kg in males. In contrast MCHC value was decreased starting at the mid dose of 1.5 mg/kg in females at the end of the dosing phase. A statistically significant decrease of hematocrit was transiently seen after 4-week treatment. Reticulocyte count showed a slight increase at Day 31 at dose levels with decreased red blood cell parameters, indicating a regenerative response. No effects were observed on white cell parameters or on blood coagulation parameters up to the high dose in males and females.
Clinical chemistry	Concentration of triglycerides was decreased at the end of the study and concentration of urea was increased at all time points in females of the high dose group of 5 mg/kg. Blood creatinine levels did not show any significant changes. The concentration of sodium was decreased on day 87 in all male groups and starting at the mid dose of 5 mg/kg at the end of the study. Furthermore, concentration of potassium was increased in females at the high dose of 5 mg/kg on day 32, starting at the mid dose of 1.5 mg/kg on day 88 and starting at the low dose of 0.5 mg/kg on day 179. In males, potassium was transiently decreased after 3 months treatment. Concentration of calcium was increased in all treated groups of males on day 31 and starting at 5 mg/kg at the other two time points and in all treated groups of females on day 32 and 88, but not on day 179.
Urinalysis	No effects
Gross pathology	No effects
Organ weights	The weight of adrenals was increased starting at the mid dose of 5 mg/kg (absolute and relative weights) and at the high dose of 5 mg/kg in females. There was a slight decrease in the absolute weight of the seminal vesicles and kidneys in both sexes.

Parameters	Major Findings
Histopathology Adequate battery: Yes	Histopathological evaluation of adrenal glands revealed hypertrophy of the zona glomerulosa with foamy/vacuolated cytoplasm starting at the low dose in males and females. The incidences were 0/5/19/20 in males and 0/2/9/20 in females. There is also a dose-dependent increase in the severity of the findings. This is a compensatory response to the pharmacologic activity of the test article, and therefore not considered adverse. Furthermore, in exorbital lacrimal glands (males) diffuse atrophy was recorded in 2 males at the high dose of 15 mg/kg. An increased incidence of harderization was recorded in male rats starting at 1.5 mg/kg (incidences were 2/8/7/12). An increased incidence of mononuclear infiltrate was recorded in male rats starting at 1.5 mg/kg (incidences were 2/8/7/10).
[Other evaluations]	n/a

Abbreviations: ECG, electrocardiogram; MCHC, mean corpuscular hemoglobin concentration

Study Number/ Title: PH-37743 / Repeated Dose Systemic Toxicity Study in Beagle Dogs (39-Weeks Daily Administration by Gavage)

Key Study Findings

- Exaggerated pharmacological effect on histology of adrenal cortex and prostate gland weight.

Table 50. Study Information for Repeated Dose Systemic Toxicity Study in Beagle Dogs

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 0.5, 1.5 and 5 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	PEG 400
Species/strain:	Beagle dogs
Number/sex/group:	4/ sex/group
Age:	28-38 weeks
Satellite groups/unique design:	No
Deviation from study protocol affecting interpretation of results:	No

Abbreviations: GLP, good laboratory practice

Table 51. Observations and Results for Repeated Dose Systemic Toxicity Study in Beagle Dogs

Parameters	Major Findings
Mortality	None
Clinical signs	None
Body weights	None
Ophthalmoscopy	None
ECG	None
Hematology	None
Clinical chemistry	At the dose of 5 mg/kg, one male had a marginal increase in total bilirubin and one female had an increase in LDH.
Urinalysis	None
Gross pathology	Necropsy revealed a diminished size of the prostate of one male of the 1.5 mg/kg dose group and two males of the 5 mg/kg dose group, which were paralleled by decreased prostate weights at 1.5 and 5 mg/kg (see below), but without microscopic correlate.

Parameters	Major Findings
Organ weights	At the dose level of 1.5 mg/kg and higher, males showed an increase in adrenal weights and a decrease in prostate weights.
Histopathology Adequate battery: Yes	The histopathological evaluation revealed test item related findings in the adrenals in both sexes starting at the dose of 0.5 mg/kg in the form of a dose dependent increase in incidence and severity (from minimal to slight at 0.5 mg/kg to moderate to excessive at 5 mg/kg) of diffuse hyperplasia of the zona arcuata / reduced width of the zona fasciculate. This effect is considered to be an adaptive response due to the mineralocorticoid receptor antagonism of BAY 94-8862. Similar effects were observed in the 13-week dog repeat-dose toxicology study for this drug.
[Other evaluations]	n/a

Abbreviations: ECG, electrocardiogram; LDH, lactate dehydrogenase

13.1.4.2. Genetic Toxicology

Table 52. Genetic Toxicology

Study No./ Study Title	Key Study Findings
TOXT5079649/ In Vitro Reverse Mutation Assay in Bacterial cells GLP compliance: Yes Study is valid: Yes	The results of the Bacterial Reverse Mutation assay indicate that under the conditions of the study, the test article BAY 94-8862 (doses from 0.1 to 5 mg/plate) did not increase the mean number of revertants/plate with any tester strains (S. typhimurium: TA98, TA100, TA1535, TA1537 and TA102) either in the presence or absence of microsomal enzymes prepared from rat liver (S9).
T4079314/ Assay for Chromosomal Aberrations In Vitro in Chinese Hamster V79 Cells GLP compliance: Yes Study is valid: Yes	After 4 hours treatment of Chinese hamster V79 cells with BAY 94-8862 concentrations of 55, 110, and 220 µg/ml were used without S9 mix for assessment of the clastogenic potential of BAY 94-8862. With S9 mix, concentrations of 80, 160 and 350 µg/ml were used. In addition, after 18 hr treatment with BAY 94-8862 concentrations of 40, 80 and 120 µg/ml were selected for reading without S9 mix. None of these cultures treated with BAY 94-8862 in the absence or presence of S9 mix showed biologically relevant increases of numbers of metaphases with aberrations. The positive controls mitomycin C and cyclophosphamide induced clear clastogenic effects and demonstrated the sensitivity of the test system and in the case of cyclophosphamide the activity of the used S9 mix.
T2079330/ Assay for Micronucleus Induction in Rat Bone Marrow From a 2-Week Oral Toxicity Study GLP compliance: Yes Study is valid: Yes	The micronucleus test was employed to investigate BAY 94-8862 in male NMRI mice for possible clastogenic effects on the chromosomes of bone-marrow erythroblasts. The known clastogen and cytostatic agent, cyclophosphamide, served as the positive control. Mice were treated with BAY 94-8862 twice with i.p. injections. Dosages were 250, 500 and 1000 mg/kg, separated by 24 hr. Negative controls received 2 i.p. injections of vehicle. Positive controls received 1 i.p. injection of cyclophosphamide (20 mg/kg). There was a strong altered ratio between polychromatic and normochromatic erythrocytes which demonstrates adequate systemic exposure to the test article. After 2 i.p. injections of the test article at all doses, there was no indication of a clastogenic effect of BAY 94-8862. Cyclophosphamide had a clear clastogenic effect as demonstrated by an increase in polychromatic erythrocytes with micronuclei. The ratio of polychromatic to normochromatic erythrocytes was not altered.

Abbreviations: GLP, good laboratory practice; i.p., intraperitoneal

13.1.4.3. Reproductive Toxicology

Rat Embryofetal Development Toxicity Study

Study Number/ Title: T6082411/Prenatal Developmental Toxicity Study in Rats after Administration by Gavage

Key Study Findings

- Only effect observed was decreased body weight gain in dams at doses ≥10 mg/kg/day.
- GLP Compliance: Yes

Table 53. Methods of Oral Embryo-Fetal Developmental Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 3, 10 and 30 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	ethanol/Solutol® HS 15/demineralized water (1:4:5 v/v/v)
Species/strain:	Wistar rat
Number/sex/group:	22 females/group
Satellite groups:	5 females/group TK
Study design:	Dams treated once/day from gestation day 6-17
Deviation from study protocol affecting interpretation of results:	None

Abbreviations: TK, toxicokinetic

Table 54. Observations and Results of Embryo-Fetal Development Study in Rats

Parameters	Major Findings
Mortality	No effect
Clinical signs	None
Body weights	Mean body weight development and corrected body weight gain were decreased at dose levels of 10 mg/kg /day and above. During the dose period of days 6-17, 10 mg/kg/day and 30 mg/kg/day groups had decreased body weight gain by approximately 25% and 54%, respectively, compared with the vehicle control group. The decreased corrected body weight gain from days 0-21 was approximately 24% and 51%, at 10 mg/kg/day and 30 mg/kg/day, respectively, both statistically significant.
Necropsy findings Cesarean section data	The fertility rate (percentage of inseminated females with implantations), the mean numbers of corpora lutea, preimplantation losses, and implantation sites in the dose groups did not differ to a meaningful extent from the control group values. The gestation rate was unaffected by treatment at dose levels up to 30 mg/kg /day. Appearance of placentas was unaffected by treatment at dose levels up to 30 mg/kg/day, whereas placental weights were decreased at dose levels of 10 mg/kg /day and above. Postimplantation loss and number of fetuses were unaffected by treatment at dose levels up to 30 mg/kg /day. Fetal sex distribution was unaffected by treatment at dose levels up to 30 mg/kg /day. Weights of fetuses were statistically significantly decreased at dose levels of 10 mg/kg /day and above.

Parameters	Major Findings
Necropsy findings Offspring	Low dose: skeletal deviations (retardations, variations) at ≥10 mg/kg Mid dose: skeletal deviations High dose: The incidence of visceral and skeletal variations was increased (slight edema, shortened umbilical cord, slightly enlarged fontanelle) and one fetus showed complex malformations including a rare malformation (double aortic arch).

Rat Fertility and Early Embryonic Development Study

Study Number/ Title: T1076747/Study of Fertility and Early Embryonic Development in Rats After Oral Administration

Key Study Findings

- Only effects observed were decreased body weight gain in dams at doses ≥10 mg/kg/day.
- GLP Compliance: Yes

Table 55. Methods of Fertility and Early Embryonic Development Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 3, 10 and 30 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	ethanol/Solutol® HS 15/demineralized water (1:4:5 v/v/v)
Species/strain:	Wistar rat
Number/sex/group:	24 per sex/group
Satellite groups:	None
Study design:	The male rats were treated daily for 4 weeks prior to mating, during the following mating period, and up to the day before necropsy. The female rats were treated daily for 2 weeks prior to mating and during the subsequent mating period. After insemination had been verified (day 0 of gestation), treatment of the females was continued up to and including day 7 post coitum.
Deviation from study protocol affecting interpretation of results:	None

Table 56. Observations and Results of Fertility and Early Embryonic Development Study in Rats

Parameters	Major Findings
Mortality	One female in the 3 mg/kg group died most likely of an injection error.
Clinical signs	Salivation in all animals including controls.
Body weights	Statistically significant decreased mean body weight gain occurred in males at dose levels up to 30 mg/kg during the premating period (days 1-29). Final body weight in males was statistically significantly decreased at the 10 mg/kg and 30 mg/kg levels, and marginally decreased at the 3 mg/kg level. Mean body weight loss in females was evident at dose levels up to 30 mg/kg from days 1-8 of treatment during the premating period, and mean body weight gain was statistically significantly decreased in females at the 30 mg/kg level from days 0-7 post-coitum followed by a compensatory increase thereafter.
Necropsy findings Cesarean section data	Absolute and relative ovary weights were decreased at the 10 mg/kg and 30 mg/kg levels. The mean number of corpora lutea was statistically significantly decreased at the dose level of 30 mg/kg. The mean number of implantation sites was statistically significantly decreased at the dose level of 30 mg/kg, lying within the range of historical control data, related to the also decreased number of corpora lutea. The mean postimplantation loss was increased at the 30 mg/kg level, for which a treatment related effect is assumed, since this value lay above the range of historical control data of the rat strain used. The mean number of viable embryos was statistically significantly decreased at the 30 mg/kg level, corresponding to the lower number of corpora lutea and implantation sites at this dose level.
Necropsy findings Offspring	Low dose: None Mid dose: None High dose: None

Rabbit Embryofetal Development Toxicity Study

Study Number/ Title: T5082410/ Prenatal Developmental Toxicity Study in Rabbits after Administration by Gavage

Key Study Findings

- Transient decreases in body weight gain in dams.
- GLP Compliance: Yes

Table 57. Methods of Oral Embryo-Fetal Developmental Study in Rabbits

Parameter	Method Details
Dose and frequency of dosing:	0, 0.25, 0.75 and 2.5 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	0.5% aqueous Tylose MH 300 P2 (methylhydroxyethylcellulose)
Species/strain:	Rabbit/ CHBB:HM
Number/sex/group:	20 females/group
Satellite groups:	3 females/group TK
Study design:	Dams treated once/day from gestation day 6-20 post coitum
Deviation from study protocol affecting interpretation of results:	None

Abbreviations: TK, toxicokinetic

Table 58. Observations and Results of Embryo-Fetal Developmental Study in Rabbits

Parameters	Major Findings
Mortality	No effect
Clinical signs	One female (no. 1406) was found dead (see above) on day 24 p.c. after it had shown transient body weight loss, reduced amounts of feces, decreased water consumption and thus decreased urination, and reddish excretion, for which a treatment related effect cannot totally be excluded. One female (no. 1392) of the 0.25 mg/kg group revealed an abortion on day 26 p.c. after it had shown severe body weight loss (-233 g during the treatment period), markedly decreased to no food intake, reduced amount of feces, decreased water consumption and thus decreased and discolored urination. Necropsy showed a cecum with gaseous contents, greenish discoloration of the liver in the area of the gall bladder, and gall bladder fused with the abdominal wall.
Body weights	Mean body weight gain was decreased between days 6-9 p.c. at the 2.5 mg/kg level. A treatment related effect on decreased mean body weight development between days 8-9 p.c. at the 0.25 mg/kg and 0.75 mg/kg levels is not assumed, since only a single day interval was affected, and because absolute main body weight gain during gestation was unaffected at these dose levels. Corrected body weight gain was unaffected at dose levels up to 2.5 mg/kg. Thus, mean body weight gain was decreased between days 6-9 p.c. at the 2.5 mg/kg level. Corrected body weight gain was unaffected at dose levels up to 2.5 mg/kg.
Necropsy findings Cesarean section data	The mean numbers of corpora lutea, preimplantation losses, and implantation sites in the dose groups did not differ from the control group values. The gestation rate is not affected at dose levels up to 2.5 mg/kg /day. The placental weights were unaffected by treatment at dose levels up to 2.5 mg/kg/day. Postimplantation loss and number of fetuses were unaffected by treatment at dose levels up to 2.5 mg/kg/day.
Necropsy findings Offspring	Low dose: None Mid dose: None High dose: None

Abbreviations: p.c., post coitum

Rat Pre- and Postnatal Development Study

Study Number/ Title: T103803-5 /BAY 94-8862: Oral (Gavage) Study of Pre- and Postnatal Development in the Rat

Key Study Findings

- Increased pup mortality at 3 and 10 mg/kg/day
- Kidney histopathology in pups at 3 and 10 mg/kg/day
- GLP Compliance: Yes

Table 59. Methods of Oral PPND Study in Rats

Parameter	Method Details
Dose and frequency of dosing:	0, 1, 3 and 10 mg/kg/day
Route of administration:	Oral gavage
Formulation/vehicle:	Ethanol/Kolliphor HS15/Water (10/40/50 v/v/v)
Species/strain:	Wistar rat
Number/sex/group:	22 females/group 20 F1 offspring/group
Satellite groups:	None
Study design:	Dams treated once/day from GD 6-LD 21
Deviation from study protocol affecting interpretation of results:	None

Abbreviations: GD, gestation day; LD, lactation day; PPND, pre- and postnatal development

Table 60. Observations and Results of PPND Study in Rats

Parameters	Major Findings
Mortality	Four pups from two litters exposed to 10 mg/kg/day, four pups from four litters exposed to 3 mg/kg/day were found dead or missing (presumed cannibalized).
Clinical signs	None
Body weights	Test item-related body weight losses were observed after the first dosing occasion of 3 or 10 mg/kg/day, which resulted in lower mean body weights for these groups during gestation. Mean body weight change was significantly lower from GD 6 to 20 for all test item-treated groups, compared with controls, and a dose response was evident. These changes were accompanied by lower mean food consumption, compared with controls. Mean body weights were still lower from LD 0 up to LD 21 for dams of the group administered 10 mg/kg/day, although mean body weight gain from LD 1 to 21 was however significantly higher, compared with controls. No such effects were noted following 1 or 3 mg/kg/day during lactation. Marginally lower mean food consumption was also observed following administration of 3 mg/kg/day, compared with controls. In F1 pups, Mean pup body weights were lower than controls following maternal administration of 10 mg/kg/day. Lower mean pup body weights were also evident on PND 1 for pups maternally administered 3 or 1 mg/kg/day, compared with controls; however, mean values were essentially similar to control by PND 21.

Parameters	Major Findings
Necropsy findings Cesarean section data	18, 22, 21, and 22 dams administered control item (vehicle) or 1, 3, or 10 mg/kg/day, respectively, were pregnant and delivered live offspring. The numbers of stillbirths were higher for 10 mg/kg/day litters compared with controls. Pup mortality between PND 0 to 4 was higher in litters from 3 or 10 mg/kg/day. F1: Pinna unfolding was delayed for pups maternally exposed to 10 mg/kg/day, compared with controls. Lower mean body weights and body weight change were evident throughout the F1 phase for both sexes previously exposed to 10 mg/kg/day. Test item-related increases in total activity, mobile counts and rears were evident for males or females maternally exposed with 10 or 3 mg/kg/day.
Necropsy findings Offspring	Low dose: Pale kidney, slight mottled kidneys Mid dose: Pale kidney, slight mottled kidneys High dose: A higher incidence of pale kidneys was observed for males maternally exposed to 10 mg/kg/day

Abbreviations: GD, gestation day; LD, lactation day; PND, postnatal day; PPND, pre- and postnatal development

13.1.4.4. Juvenile Toxicology Study

General Juvenile Toxicology Study

Juvenile Wistar rats were treated with 0, 1, 3 and 10 mg/kg/day (once/day by oral gavage) starting on PND 14. A 4-week recovery group was included to assess recovery from any observed toxicity.

The only effects that were observed included those associated with the pharmacological effects of the drug. These included reversible hypertrophy of the zona glomerulosa of the adrenal cortex (in both sexes at 1 mg/kg/day), reversible hypertrophy of the zona fasciculata of the adrenal cortex (in males at 10 mg/kg/day) and vacuolation of the zona glomerulosa (in both sexes at 10 mg/kg/day in recovery animals).

The NOAEL was considered to be 10 mg/kg/day since all effects observed were attributable to the pharmacological effect of finerenone. There was no impact on the development milestones including bone measurement. There was no indication of any new target organs of toxicities or higher sensitivity of juvenile animals compared with adolescent/adult animals.

Reproductive Juvenile Toxicology Study

Because of findings in female reproductive organs in general toxicology studies, female fertility was also assessed in juvenile rats in a separate study. Female juvenile Wistar rats were treated with 0, 1, 3 and 10 mg/kg/day (once/day by oral gavage) starting on PND 14 for 13 weeks.

Like in the general toxicology studies, compensatory effects on the adrenal cortex were observed. Most importantly, no effects on fertility were observed up to the high dose of 10 mg/kg. The NOAEL was thus 10 mg/kg/day.

13.1.5. Impurities/Degradants

Impurities and degradants were not an issue with this application. No toxicological studies with isolated impurities of finerenone were performed. The batches used in toxicological studies provided support of the specifications used during clinical development.

13.1.5.1. Metabolites

A clinical study with single oral administration of [14C]finerenone showed that in human plasma, the naphthyridine metabolites M-1, M-2, and M-3 were the predominant plasma metabolites covering 49%, 22%, and 9% AUC of total radioactivity. Detailed investigations revealed that these metabolites exhibited axial chirality forming the atropisomers M-1a, M-1b, M-2a, M-2b, M-3a and M-3b. Analysis of plasma and/or urine samples of rat, dog, and human showed the predominant formation of one atropisomer ("a" series, >80%) of each metabolite across all species. It was also determined that metabolites M-1a, M-1b, M-2a and M-3a are major human metabolites. All major human plasma metabolites were not pharmacologically active against the MR and demonstrated no relevant off-target activities.

Based on the exposure data calculated for the individual atropisomers BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a) and BAY 1117271 (M-3a), an adequate exposure of each individual major human metabolites was considered to have been achieved in rats to assess repeat-dose toxicity, carcinogenicity and embryo-fetal developmental toxicity of these metabolites (Table 61 to Table 64). Therefore, these major human metabolites were considered qualified from a nonclinical perspective. Of note, the exposure comparisons across species was conducted at the high dose (maximum tolerated dose) in the animal studies compared to the maximum exposure in humans at the therapeutic dose.

Table 61. Overview on Systemic Exposure of BAY 1117267 (M-1a) at Steady State in Toxicology Studies and Multiples of Exposure Compared to Human Exposure at MRHD

Daily dose		Total exposure				Unbound exposure[a]			
		C_{max}		AUC(0-24)		$C_{max,\,u}$		$AUC(0\text{-}24)_u$	
[mg/kg/day]	Sex	[µg/L]	MoE	[µg·h/L]	MoE	[µg/L]	MoE	[µg·h/L]	MoE
13-week study in rats									
30.0	M	1621	5.4	16443	3.3	97.4	5.5	988.2	3.4
30.0	F	738	2.4	7046	1.4	44.4	2.5	423.5	1.5
26-week study in rats									
15.0	M	1020	3.4	15777	3.2	61.3	3.5	948.2	3.3
5.0	F	92	0.3	1804	0.4	5.5	0.3	108.4	0.4
Carcinogenicity study in rats									
20	M	1376	4.5	21934	4.4	82.7	4.7	1318.2	4.6
10	F	132	0.4	2175	0.4	8.0	0.5	130.7	0.5
Embryo-fetal developmental toxicity study in rats									
30.0	F	729	2.4	11128	2.3	43.8	2.5	668.8	2.3
Human exposure									
20 mg od		302.48		4936.14		17.60		287.28	

MoE = margins of exposure (when compared to human plasma levels)
[a] f_u(human) = 5.82%, f_u(rat) = 6.01%
Only the highest dose for each sex in each study is listed in the table

Source: Applicant's table
Abbreviations: AUC, area under the curve; MRHD, maximum recommended human dose

Table 62. Overview on Systemic Exposure of BAY 1117266 (M-1b) at Steady State in Toxicology Studies and Multiples of Exposure Compared to Human Exposure at MRHD.

Daily dose		Total exposure				Unbound exposure[a]			
		C_{max}		AUC(0-24)		$C_{max, u}$		$AUC(0-24)_u$	
[mg/kg/day]	Sex	[µg/L]	MoE	[µg·h/L]	MoE	[µg/L]	MoE	[µg·h/L]	MoE
13-week study in rats									
30.0	M	64	1.0	649	0.6	7.1	3.0	72.1	1.9
30.0	F	137	2.2	1304	1.3	15.2	6.4	144.7	3.7
26-week study in rats									
15.0	M	40	0.7	623	0.6	4.5	1.9	69.2	1.8
5.0	F	17	0.3	334	0.3	1.9	0.8	37.1	1.0
Carcinogenicity study in rats									
20	M	54	0.9	866	0.9	6.0	2.5	96.2	2.5
10	F	24	0.4	402	0.4	2.7	1.1	44.7	1.1
Embryo-fetal developmental toxicity study in rats									
30.0	F	135	2.2	2059	2.1	15.0	6.3	228.6	5.9
Human exposure									
20 mg od		61.52		1003.86		2.39		38.95	

MoE = margins of exposure (when compared to human plasma levels)
[a] f_u(human) = 3.88%, f_u(rat) = 11.10%
Only the highest dose for each sex in each study is listed in the table
Source: Applicant's table
Abbreviations: AUC, area under the curve; MRHD, maximum recommended human dose

Table 63. Overview on Systemic Exposure of BAY 1117268 (M-2a) at Steady State in Toxicology Studies and Multiples of Exposure Compared to Human Exposure at MRHD.

Daily dose		Total exposure				Unbound exposure[a]			
		C_{max}		AUC(0-24)		$C_{max, u}$		$AUC(0-24)_u$	
[mg/kg/day]	Sex	[µg/L]	MoE	[µg·h/L]	MoE	[µg/L]	MoE	[µg·h/L]	MoE
13-week study in rats									
30.0	M	532	3.5	5434	2.0	241.7	9.1	2467.4	5.2
30.0	F	254	1.7	2371	0.9	115.2	4.3	1076.3	2.3
26-week study in rats									
15.0	M	324	2.1	4736	1.7	146.9	5.5	2149.9	4.5
5.0	F	50	0.3	651	0.2	22.8	0.9	295.8	0.6
Carcinogenicity study in rats									
20	M	440	2.9	7402	2.7	199.9	7.5	3360.6	7.1
10	F	63	0.4	1054	0.4	28.4	1.1	478.3	1.0
Embryo-fetal developmental toxicity study in rats									
30.0	F	374	2.5	5558	2.0	169.8	6.4	2523.2	5.3
Human exposure									
20 mg od		152.48		2725.58		26.53		474.25	

MoE = margins of exposure (when compared to human plasma levels)
[a] f_u(human) = 17.4%, f_u(rat) = 45.4%
Only the highest dose for each sex in each study is listed in the table
Source: Applicant's table
Abbreviations: AUC, area under the curve; MRHD, maximum recommended human dose

Table 64. Overview on Systemic Exposure of BAY 1117271 (M-3a) at Steady State in Toxicology Studies and Multiples of Exposure Compared to Human Exposure at MRHD.

Daily dose		Total exposure				Unbound exposure[a]			
		C_{max}		AUC(0-24)		$C_{max,\ u}$		$AUC(0\text{-}24)_u$	
[mg/kg/day]	Sex	[µg/L]	MoE	[µg·h/L]	MoE	[µg/L]	MoE	[µg·h/L]	MoE
13-week study in rats									
30.0	M	135	1.9	1711	1.3	100.3	2.1	1268.1	1.4
30.0	F	121	1.7	1042	0.8	89.4	1.9	771.8	0.8
26-week study in rats									
15.0	M	108	1.6	1236	0.9	80.3	1.7	916.2	1.0
5.0	F	22	0.3	192	0.1	16.6	0.4	142.4	0.2
Carcinogenicity study in rats									
20	M	172	2.5	2769	2.0	127.5	2.7	2051.6	2.2
10	F	66	1.0	844	0.6	49.2	1.0	625.4	0.7
Embryo-fetal developmental toxicity study in rats									
30.0	F	76	1.1	1126	0.8	56.0	1.2	834.7	0.9
Human exposure									
20 mg od		69.58		1356.32		47.18		919.58	

MoE = margins of exposure (when compared to human plasma levels)
[a] f_u(human) = 67.8%, f_u(rat) = 74.1%
Only the highest dose for each sex in each study is listed in the table
Source: Applicant's table
Abbreviations: AUC, area under the curve; MRHD, maximum recommended human dose

13.2. Individual Reviews of Studies Submitted to the NDA

13.2.1. Carcinogenicity

13.2.1.1. Study Title: BAY 94-8862: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Mouse

Table 65. Study Information for Study BAY 94-8862 in Mice

Study no.:	T102254-4	
Study report location:	EDR	
Study initiation date:	October 12, 2015	
GLP compliance:	Yes	Yes
Drug, lot #, and % purity:	BAY 94-8862; 84110270; 100%	
Prior Exec CAC Dose Concurrence:	Y	

Study no.:	T102254-4
Basis for Dose Selection:	The high dose selection was based on adequate AUC ratios in both males and females in a 13-week study. BAY 94-8862 was very well tolerated by mice, and was tested at dose levels of 0, 1, 3, and 10 mg/kg/day in males or 0, 0.75, 2.5, and 7.5 mg/kg/day in females in a 13-week study. The toxicological profile of BAY 94-8862 was characterized by exaggerated pharmacology and sequelae thereof. This included a compensatory hypertrophy of the zona glomerulosa of the adrenal glands and, at high exposure levels, also changes in electrolyte and water balance. In the 13-week study in mice, minor changes were also noted in the testis and epididymides. Although the high-dose level in the current study (30 mg/kg/day) was expected to be well tolerated, additional body weight monitoring was undertaken at this dose level (and 10 mg/kg/day for males or 7.5 mg/kg/day for females) over the first week of dosing, as a precaution. The dose selection in a Special Protocol Assessment was agreed by the CDER exec CAC (see SPA agreement in DARRTS dated June 25, 2015 under IND-117847).

Abbreviations: AUC, area under the curve; CAC, carcinogenicity assessment committee; DARRTS, Document Archiving, Reporting and Regulatory Tracking Systems; GLP, good laboratory practice; SPA, special protocol assessment

Reviewer Carcinogenicity Conclusion: Negative

ECAC Carcinogenicity Conclusion: ***Negative***

Tumor Findings

Upon microscopic examination, BAY 94-8862-related neoplastic findings were recorded for the testis, for which an increased incidence of Leydig cell adenoma was recorded for males administered 30 mg/kg/day. The numerical increase in Leydig cell adenoma may have a relationship to drug treatment but did not reach FDA's threshold for statistical significance.

Table 66. Toxicity Experimental Design for Study BAY 94-8862 in Mice

Table 3: Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)			
	Male	Female		Male (Group #)		Female (Group #)	
1	60	60	Vehicle control	0	Group 0	0	Group 0
2	60	60	Saline control	0	Group 1	0	Group 1
3	60	60	BAY 94-8862 Low	1	Group 3	0.75	Group 2
4	60	60	BAY 94-8862 Mid	3	Group 5	2.5	Group 4
5	60	60	BAY 94-8862 Mid-High	10	Group 7		
6	60	60	BAY 94-8862 High	30	Group 8	7.5	Group 6

Source: Applicant's table

Table 67. Methods for Study BAY 94-8862 in Mice

Parameter	Method Details
Frequency of dosing:	Once/day
Dose volume:	10 ml/kg
Formulation/Vehicle:	Aqueous 0.5% Tylose®, prepared by (b) (4) using Tylose MH300®, supplied by
Route of administration:	ORAL GAVAGE
Species:	MOUSE
Strain:	CD1(ICR)
Age:	7-8 weeks old at start of dosing
Comment on Study Design and Conduct:	None
Dosing Comments (Dose Adjustments or Early Termination):	None
Dosing Solution Analysis:	The mean % nominal concentration was targeted between 80 and 120% with a coefficient of variation of ≤6.0%. Results were within these criteria and considered homogeneous and of acceptable concentration.

Statistical Criteria for Evaluation of Tumor Data

Both the trend and pairwise analysis should be significant.

For common tumors (>1%):

- P<0.005 by Trend Analysis
- P<0.01 for Pairwise

For rare tumors (<1%):

- P<0.025 by Trend Analysis
- P<0.05 by Pairwise

Observations and Results

Mortality

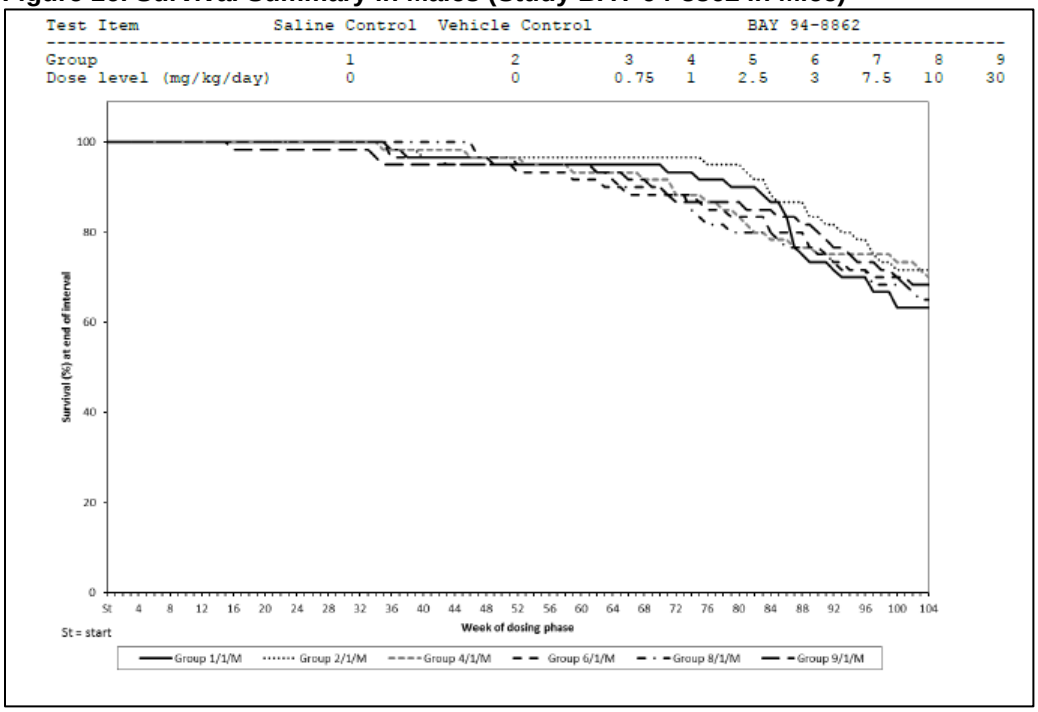
A sufficient number of animals survived an appropriate duration to result in acceptable exposure to BAY 94-8862 for a valid evaluation of the carcinogenic potential of BAY 94-8862 (Table 68, Figure 16, and Figure 17.

Table 68. Group Mortality Incidence-Carcinogenicity Animals (Study BAY 94-8862 in Mice)

Sex	Males						Females				
Dose Level (mg/kg/day)	0	0	1	3	10	30	0	0	0.75	2.5	7.5
Total number of animals on study	60	60	60	60	60	60	60	60	60	60	60
Total number of decedent animals	22	19	18	19	21	20	36	31	29	34	34
Total number at terminal kill	38	41	42	41	39	40	24	29	31	26	26

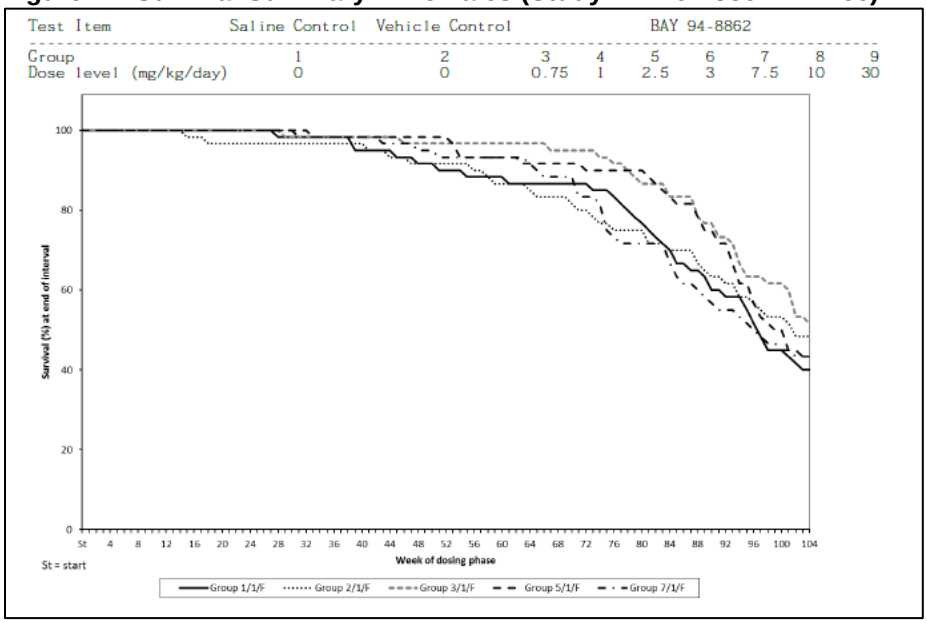
Source: Applicant's table

Figure 16. Survival Summary in Males (Study BAY 94-8862 in Mice)



Source: Applicant's table

Figure 17. Survival Summary in Females (Study BAY 94-8862 in Mice)



Source: Applicant's table

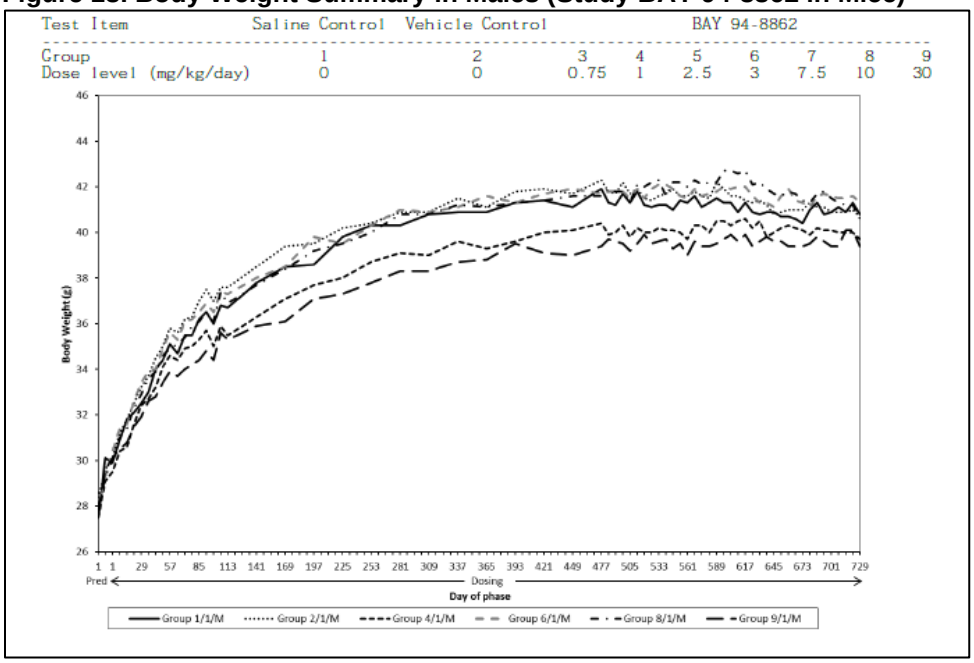
Clinical Signs

No BAY 94-8862-related clinical observations were noted.

Body Weights

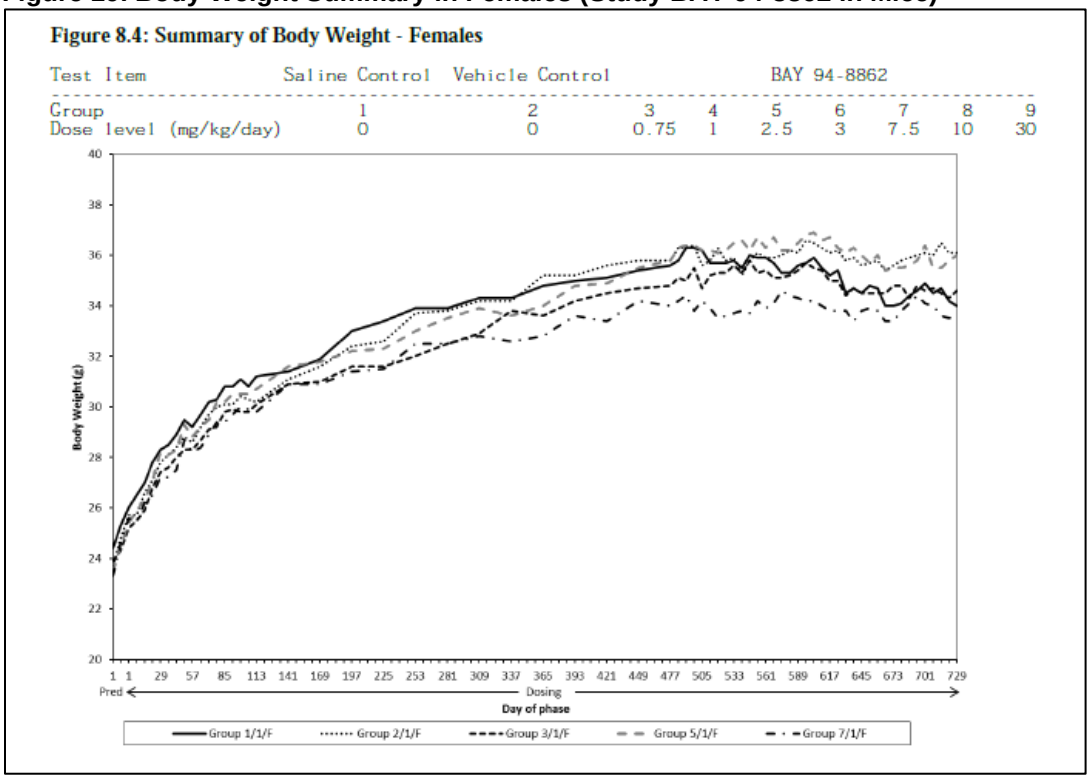
Administration of BAY 94-8862 resulted in statistically significantly lower mean body weight gain (by 35%; but not body weight loss) from Days 1 to 92 for males administered 30 mg/kg/day (Figure 18). Thereafter, mean body weight gain for these animals was comparable with controls for the remaining duration of the dosing phase. No associated reduction in food consumption was noted over this time.

Figure 18. Body Weight Summary in Males (Study BAY 94-8862 in Mice)



Source: Applicant's table

Figure 19. Body Weight Summary in Females (Study BAY 94-8862 in Mice)



Source: Applicant's table

Feed Consumption

No BAY 94-8862-related effect was noted on food consumption.

Gross Pathology

Upon macroscopic examination, BAY 94-8862-related findings were noted in the testis only. In this tissue, pale area and/or macroscopic enlargement were recorded for some males administered 3, 10, or 30 mg/kg/day, which generally correlated with microscopic findings (Table 69).

Table 69. Summary of Testicular Gross Pathology (Study BAY 94-8862 in Mice)

		Males					
		1M	2M	4M	6M	8M	9M
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	30
Testis	No. examined:	60	60	60	60	60	60
pale area	-	60	60	60	58	60	54
	P	0	0	0	2	0	6
large	-	60	60	60	58	59	59
	P	0	0	0	2	1	1

Source: Applicant's table
Abbreviations: -, finding not present; P, finding present; M, male

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: Yes

All carcinogenicity animals and all unscheduled deaths/sacrifices in the satellite and carcinogenicity animals were subject to necropsy. All carcinogenicity animals that died or were sacrificed following the commencement of the scheduled necropsy (Day 729 or 730 of the dosing phase for females and males, respectively) were marked as terminal sacrifice. The scheduled necropsies were performed on Days 729 to 742 of the dosing phase. Where possible, they were carried out in replicate order. Each animal was administered isoflurane anesthesia. Once a suitable deep plane of anesthesia was established, the animal was exsanguinated by severing major blood vessels. Animals were weighed before necropsy. The organs denoted by *W* in the tissue list from all carcinogenicity animals, excluding decedent animals, were dissected, freed from fat and other contiguous tissue, and weighed before fixation. Left and right organs were weighed together. A full macroscopic examination was performed under the general supervision of a Pathologist, and all lesions were recorded. The following tissues from each animal were preserved in 10% neutral-buffered formalin unless otherwise indicated (Table 70).

Table 70. Tissues Undergoing Histopathology (Study BAY 94-8862 in Mice)

Organ/Tissue			Organ/Tissue		
adrenal	W	E	nerve, optic		E
animal identification			nerve, sciatic		E
aorta		E	nose/nares		
bone marrow smear (femur)[a]			ovary		E
brain	W	E	oviduct		E
cecum		E	pancreas		E
colon		E	parotid salivary gland		E
duodenum		E	pituitary		E
esophagus		E	preputial/clitoral gland		E
eye[b]		E	prostate		E
femur with bone marrow (tissue includes femoro-tibial joint)		E	rectum		E
gall bladder		E	seminal vesicle with coagulation glands		E
gross lesions		E	skin and subcutis		E
Harderian gland[c]		E	spinal cord, cervical		E
head			spinal cord, lumbar		E
heart	W	E	spinal cord, thoracic		E
ileum		E	spleen	W	E
jejunum		E	sternum with bone marrow		E
kidney	W	E	stomach		E
lacrimal gland		E	sublingual salivary gland		E

Organ/Tissue			Organ/Tissue		
larynx		E	testis and epididymis[d]	We	E
liver	W	E	thymus		E
lungs (includes main stem bronchi and bronchioles)		E	thyroid with parathyroid		E
lymph node, iliac		E	tissue masses		E
lymph node, mandibular		E	tongue		E
lymph node, mesenteric		E	trachea		E
mammary gland		E	ureter		E
mandibular salivary gland		E	urethra		
mesentery		E	urinary bladder		E
muscle, quadriceps		E	uterus with cervix	W	E
nasal cavity		E	vagina		E
nasopharynx			Zymbal's gland		E

W = weighed; E = tissues processed and examined microscopically.
Note: Bone tissue designated for microscopic examination was decalcified using Kristenson's fluid.
a Smear prepared; air dried, then fixed in methanol. Samples were not taken from animals dead prior to necropsy. See Bone Marrow Smear Evaluation.
b Tissue taken into Davidson's fixative.
c Preserved with the head (*in situ*).
d Tissue taken into Modified Davidsons fixative and processed to at least the block stage.
e Tissues weighed together.

Source: Applicant's table

Neoplastic

In the testis, an increased incidence of Leydig cell adenoma was recorded for males administered 30 mg/kg/day BAY 94-8862 (Table 71), which generally correlated with findings recorded macroscopically. No concomitant increase in focal or diffuse Leydig cell hyperplasia was present. A statistically significant positive trend in Leydig cell adenoma incidences (P-value 0.0002 by sponsor analysis and P-value 0.0007 by FDA statistical reviewer analysis) and a significant difference in the pairwise vehicle control versus 30 mg/kg/day values (P-value 0.0149 by sponsor analysis and P-value 0.0256 by FDA statistical reviewer analysis) were reported (Table 72 and Table 73). Leydig cell adenoma were characterized by a mass of cells in the testis, located between and compressing, surrounding seminiferous tubules, with abundant, finely vacuolated/granular eosinophilic cytoplasm and larger than the diameter of three seminiferous tubules. Leydig cell adenoma were present unilaterally in all animals, and with the exception of one animal administered 1 mg/kg/day, in those surviving to the terminal sacrifice.

Leydig cell adenoma is considered a common tumor with a (b) (4) historical control incidence of 4.7% (2008 - 2013) and 3.2% (2013 - 2018). A statistically significant dose response relationship (p-value=0.0007) was noted for leydig cell adenoma in testis of male mice. Although there is an increased incidence of this tumor in the 30 mg/kg/day group compared with the vehicle control group, the P value of the pairwise analysis did not achieve statistical significance for common tumors (P value should be less than 0.01 for Pairwise analysis to be considered statistically significant for a common tumor type, per the current FDA guidelines (May 2001)). Mechanistically, compensatory Leydig cell hyperplasia and/or neoplasia have been described as a result of androgen receptor antagonism (Greaves 2012), although no increase in Leydig cell hyperplasia was reported in this study. Based on the statistically significant dose response relationship, the reviewing pharmacologist considers the occurrence of Leydig cell adenoma to be related to BAY 94-8862 administration.

Table 71. Incidence of Selected Findings; Testis-All Carcinogenicity Animals (Study BAY 94-8862 in Mice)

		Decedent Males					
		1M	2M	4M	6M	8M	9M
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	30
Testis	No. examined:	22	19	18	19	21	20
Leydig cell adenoma	-	22	19	17	19	21	20
	P	0	0	1	0	0	0
		Terminal Kill Males					
		1M	2M	4M	6M	8M	9M
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	30
Testis	No. examined:	38	41	42	41	39	40
Leydig cell adenoma	-	36	40	42	38	39	31
	P	2	1	0	3	0	9

- = Finding not present; P = Finding present. M = Male.

Source: Applicant's table

Table 72. Results of Statistical Analyses of Neoplastic Lesions (Study BAY 94-8862 in Mice)

Tissue and Lesion	Rare or Common	Comparison	Incidence	P-value	FDA Interpretation
Testis	Common	Trend	2/60,1/60,3/60,0/60,9/60	0.0002	Significant
B-Leydig cell adenoma					(p<0.005)
		Group 1 v 9	2/60 v 9/60	0.0149	Not significant (p≥0.01)

Source: Applicant's table

Table 73. Summary Table of Tumor Types With P-Values ≤0.05 for Dose-Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Study BAY 94-8862 in Mice

Organ name	Tumor name	Vehicle (C) 0 mg P-Trend	Low (L) 1 mg LP-LvsC	Mid (M) 3 mg P-MvsC	Mid-High (MH) 10 mg P-MHvsC	High (H) 30 mg P-HvsC	Saline (S) P-SvsC
Male							
Testis	B-Leydig Cell Adenoma	2/60 (50) &	1/60 (50)	3/60 (49)	0/60 (49)	9/60 (50)	1/60 (53)
		0.0007 $	0.8788	0.4903	1.0000	0.0256 x	0.8892

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.75 mg P - VC vs. L	Mid (M) 2.5 mg P - VC vs. M	High (H) 7.5 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Female						
Uterus	M-Sarcoma, Endometrial	3/60 (43)	12/60 (51)	3/60 (47)	4/60 (42)	10/60 (44)
	Stro*/B-Polyp, Endometrial	0.7851	0.0263 @	0.7033	0.4866	0.0376 @

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.
$ = Statistically significant in common tumor at 0.005 level for test of dose response relationship;
@ = Not statistically significant in common tumor at 0.01 level for test of pairwise comparisons;

Source: Statistical reviewer's table

Statistically significant increases were present in combined hemolymphoreticular tumors (females, vehicle control versus 2.5 mg/kg/day, P-value 0.0249) and combined uterine stromal tumors (females, vehicle control versus 0.75 mg/kg/day, P-value 0.0139). However, since these increases were not present in animals administered 7.5 mg/kg/day and/or only present in one sex, they were considered not toxicologically significant.

Based on the above findings, 10 mg/kg/day (males) and 7.5 mg/kg/day (females) were concluded as the NOAELs without any evidence of a carcinogenic effect. These dose levels corresponded to mean C_{max} and $AUC_{(0-24)}$ values of 97,700 µg/L and 1,190,000 µg hr/L, respectively, for males and 87,700 µg/L and 1,380,000 µg hr/L, respectively, for females on Day 365.

Non Neoplastic

In the adrenal, a decreased incidence and severity of type A subcapsular cell hyperplasia was present in males administered 10 or 30 mg/kg/day and females administered 7.5 mg/kg/day. In addition, a statistically significant dose response (both sexes, P≤0.001) and decreases between vehicle controls versus 30 mg/kg/day (males, P-value 0.0091) and vehicle controls versus 7.5 mg/kg/day (females, P<0.001) were noted. Type A subcapsular cell hyperplasia was characterized, at low severity grades, by focal proliferation of predominantly Type A cells in the subcapsular region of the adrenal. Type A cells are small, oval to spindle-shaped cells with scant basophilic cytoplasm. At higher severity grades, expansion in parallel to the capsule, potentially extending to be circumferential as well as toward the medulla, occurs and few Type B cells may be present.

Similarly, a decreased incidence and/or severity of mixed type subcapsular cell hyperplasia was present in all test item-treated male groups and in females administered 2.5 or 7.5 mg/kg/day. Mixed type subcapsular cell hyperplasia was similarly characterized; however, the cellular make up was Type A and Type B cells in similar proportions. Type B cells are large, polygonal cells with clear cytoplasm and small lipid vacuoles.

In addition, a decreased incidence and severity of focal microvesicular vacuolation was present in males administered 3, 10, or 30 mg/kg/day. In males, a statistically significant dose response (P-value 0.0031) and decreases between vehicle controls versus 10 mg/kg/day (P-value 0.0166) and vehicle controls versus 30 mg/kg/day (P-value 0.0166) were noted. Focal microvesicular vacuolation was characterized by discrete foci of increased cytoplasmic microvesicular vacuolation (small, foamy, and clear vesicles) of cortical cells of the adrenal.

See Table 74 for details.

Table 74. Adrenal Gland Histopathology (Study BAY 94-8862 in Mice)

		Males					
		1M	2M	4M	6M	8M	9M
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	30
Adrenal	No. examined:	59	58	60	59	60	60
hyperplasia, subcapsular cell, Type A	Grade -	35	35	33	27	44	49
	1	12	10	17	14	10	8
	2	9	11	9	14	6	3
	3	2	1	1	3	0	0
	4	1	1	0	1	0	0
hyperplasia, subcapsular cell, mixed type	Grade -	55	55	60	59	59	60
	1	0	0	0	0	1	0
	2	1	1	0	0	0	0
	3	2	1	0	0	0	0
	4	1	1	0	0	0	0

- = Finding not present; 1 = Minimal, 2 = Slight, 3 = Moderate, 4 = Marked; M = Males; F = Female.

Carcinogenicity Animals

		Males					
		1M	2M	4M	6M	8M	9M
Tissue and finding	Level (mg/kg/day)	0	0	1	3	10	30
Adrenal	No. examined:	59	58	60	59	60	60
microvesicular vacuolation, cortical, increased, focal	Grade -	51	40	49	55	59	59
	1	1	1	1	1	0	0
	2	6	6	5	3	1	0
	3	1	10	5	0	0	1
	4	0	1	0	0	0	0
		Females					
		1F	2F	3F	5F	7F	
Tissue and finding	Level (mg/kg/day)	0	0	0.75	2.5	7.5	
Adrenal	No. examined:	60	60	60	60	60	
hyperplasia, subcapsular cell, Type A	Grade -	2	1	1	7	32	
	1	16	19	25	34	24	
	2	34	34	31	18	4	
	3	7	6	3	1	0	
	4	1	0	0	0	0	
hyperplasia, subcapsular cell, mixed type	Grade -	60	59	59	60	60	
	1	0	0	0	0	0	
	2	0	1	0	0	0	
	3	0	0	1	0	0	

- = Finding not present; 1 = Minimal, 2 = Slight, 3 = Moderate, 4 = Marked; M = Males; F = Female.

Source: Applicant's table

Toxicokinetics

Dependence on Sex

Between male and female groups, differences in terms of $AUC_{0\text{-}24norm}$ and $C_{max,norm}$ were observed on Days 1, 176, and 365. The $AUC_{0\text{-}24norm}$ and $C_{max,norm}$ of the parent compound were, in most cases, slightly higher (1.0- to 1.3-fold on Day 1, 1.2- to 1.7-fold on Day 176, and 1.2- to 1.6-fold on Day 365) in female groups compared to male groups.

In accordance with the lower dose-normalized exposure ($AUC_{0\text{-}24norm}$ and $C_{max,norm}$) of the parent compound in males, the dose-normalized exposure of all three metabolites was higher in males than in females on all study days (Days 1, 176, and 365), except for M-2 on Days 176 and 365 (the exposure was similar to, or slightly higher than, that in females).

Dose-Dependence

In males, on Day 1, exposure ($AUC_{0\text{-}24}$ and C_{max}) of the parent compound increased dose-proportionally with the increase in dose from 1 to 10 mg/kg/day and moderately less-than-dose proportionally from 10 to 30 mg/kg/day. In females, on Day 1, the exposure of the parent compound increased dose-proportionally over the range from 0.75 to 7.5 mg/kg/day.

On Days 176 and 365, exposure of the parent compound increased dose-proportionally with the increase in dose from 1 to 3 mg/kg/day and considerably less-than-dose proportionally from 3 to 30 mg/kg/day in males. In females, exposure also increased dose-proportionally with the increase in dose from 0.75 to 2.5 mg/kg/day and slightly or moderately less-than-dose proportionally from 2.5 to 7.5 mg/kg/day.

For the metabolites M-1, M-2, and M-3, plasma concentrations increased with the increase in dose, but not dose-proportionally.

Time Course Within the Dosing Interval

The C_{max} of the parent compound was observed between 0.5 and 4 hours in females and between 0.5 and 1 hours in males summarized over Days 1, 176, and 365. The residual concentrations of BAY 94-8862 determined in samples obtained 24 hours after administration were high on all study days and amounted to 35 to 42% (Day 1), 24 to 59% (Day 176), and 46 to 58% (Day 365) of the C_{max} in females. In males, the residual concentrations were slightly lower in accordance with the slightly lower exposure compared to females. They amounted to 23 to 31% of the C_{max} on Day 1, 24 to 30% of the C_{max} on Day 176, and 24 to 36% of the C_{max} on Day 365. The C_{max} of the metabolites M-1, M-2, and M-3 was observed in the time interval between 0.5 to 2 hours after administration. Residual concentrations obtained 24 hours after administration amounted to 2.6 to 29% for males and 12 to 40% for females.

Influence of Repeated Dosing

The exposure of the parent compound in terms of $AUC_{0\text{-}24}$ and C_{max} was clearly higher after multiple dose administration (Days 176 and 365) over the tested dose range in the females (1.3- to 2.4-fold) and in the males for the doses from 1 to 10 mg/kg/day (1.1- to 1.7-fold) whereas for the highest dose of 30 mg/kg/day in the males a change in exposure on both study days compared to Day 1 was not observed.

For metabolites, exposure ($AUC_{0\text{-}24}$ and C_{max}) was also higher, in most cases after multiple doses, on Days 176 and 365 compared with Day 1 (up to 2-fold for M-1, up to 4-fold for M-2, and up to

4-fold for M-3). Exposure ratio was slightly higher on Day 365 compared to Day 176; however, metabolite plasma concentration altogether was very low compared to plasma concentrations of the parent compound.

Metabolic Ratio

The relative exposure (AUC_{0-24}) of the metabolites M-1, M-2, and M-3 was very low (<1% of the exposure of the parent compound) on Days 1, 176, and Day 365.

TK Data From Day 365

Table 75. Toxicokinetics of Parent Compound on Day 365 in Males (Study BAY 94-8862 in Mice)

Text Table 1.1: Systemic Exposure Summary of BAY 94-8862 on Day 365 - Males

Dose Parameter	(mg/kg/day) Unit	1 gMean	3 gMean	10 gMean	30 gMean
AUC_{0-24}	µg·h/L	177000	519000	1190000	1830000
$AUC_{0-24norm}$	kg·h/L	177	173	119	61.0
C_{max}	µg/L	13500	34100	97700	135000
$C_{max,norm}$	kg/L	13.5	11.4	9.77	4.49
T_{max}	h	0.500	1.00	1.00	0.500
$C(24)/C_{max}$	%	28.8	36.2	24.0	27.1
AR AUC_{0-24}	%	161.8	144.6	110.3	94.4
AR C_{max}	%	155.4	140.0	123.3	92.3

AR = Accumulation ratio; AUC_{0-24} = Area under the concentration-time curve from 0 to 24 hours postdose; C_{max} = Maximum observed concentration; Tmax = Time of C_{max}.

Source: Applicant's table

Table 76. Systemic Exposure of Parent Compound on Day 365 in Females (Study BAY 94-8862 in Mice)

Text Table 1.2: Systemic Exposure Summary of BAY 94-8862 on Day 365 - Females

Dose Parameter	(mg/kg/day) Unit	0.75 gMean	2.5 gMean	7.5 gMean
AUC_{0-24}	µg·h/L	190000	661000	1380000
$AUC_{0-24norm}$	kg·h/L	254	264	185
C_{max}	µg/L	12500	34800	87700
$C_{max,norm}$	kg/L	16.7	13.9	11.7
T_{max}	h	2.00	2.00	0.500
$C(24)/C_{max}$	%	46.5	58.2	46.1
AR AUC_{0-24}[a]	%	203.6	197.3	132.2
AR C_{max}[b]	%	189.8	160.5	137.8

AR = Accumulation ratio; AUC_{0-24} = Area under the concentration-time curve from 0 to 24 hours postdose; C_{max} = Maximum observed concentration; T_{max} = Time of C_{max}.

a Ratio of AUC0-24 from Day 365 to Day 1.

b Ratio of C_{max} from Day 365 to Day 1.

Source: Applicant's table

13.2.1.2. Study Title: BAY 94-8862: 104 Week Oral (Gavage) Administration Carcinogenicity Study in the Rat

Table 77. Study Information for Study BAY 94-8862 in Rats

Study no.:	T102253-3
Study report location:	EDR
Study initiation date:	October 9, 2015
GLP compliance:	Yes
Drug, lot #, and % purity:	BAY 94-8862; 84110270; 99.5%
Prior Exec CAC Dose Concurrence:	Y
Basis for Dose Selection:	The high dose levels of 20 mg/kg/day in males and 10 mg/kg/day in females represent the maximum-tolerated dose for carcinogenicity studies, as 30 mg/kg/day resulted in a reduced body weight gain of more than 10% in the 13-week study. These doses should result in multiples of exposure of about 10- to 20-fold the exposure at the maximum recommended human dose (MRHD) in human subjects. In addition, these dose levels should also allow sufficient coverage of the relevant metabolites. The dose selection in a Special Protocol\Assessment was agreed by the CDER exec CAC (see SPA agreement in DARRTS dated 6/25/2015 under IND-117847).

Abbreviations: CAC, carcinogenicity assessment committee; DARRTS, Document Archiving, Reporting and Regulatory Tracking Systems; GLP, good laboratory practice; SPA, special protocol assessment

Reviewer Carcinogenicity Conclusion (negative/ positive): Negative

ECAC Carcinogenicity Conclusion (negative/ positive): ***Negative***

Tumor Findings

None

Table 78. Methods for Study BAY 94-8862 in Rats

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)			
	Male	Female		Male (Group #)		Female (Group #)	
1	60	60	Vehicle control	0	Group 0	0	Group 0
2	60	60	Saline control	0	Group 1	0	Group 1
3	60	60	BAY 94-8862 Low	2	Group 3	1	Group 2
4	60	60	BAY 94-8862 Mid	6	Group 5	3	Group 4
5	60	60	BAY 94-8862 High	20	Group 7	10	Group 6

Source: Applicant's table

Table 79. Methods for Study BAY 94-8862 in Rats

Parameter	Method Details
Dose volume:	10 ml/kg
Formulation/Vehicle:	Ethanol/Kolliphore HS 15®/purified water
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR HAN
Age:	5-6 weeks of age at start of dosing
Comment on Study Design and Conduct:	None
Dosing Comments (Dose Adjustments or Early Termination):	None
Dosing Solution Analysis:	Formulations prepared for use during Weeks 1, 13, 26, 39, 52, 65, 78, 91, and 104 were analyzed to determine the achieved concentration. The % nominal concentration was targeted between 80 to 120%. Results ranged from 102 to 113% of the nominal concentration and met the acceptance criteria.

Observations and Results

Mortality

A sufficient number of animals survived an appropriate duration to result in acceptable exposure to BAY 94-8862 for a valid evaluation of the carcinogenic potential of BAY 94-8862 (Table 80, Figure 20, and Figure 21).

Table 80. Survival of Animals During Study (Study BAY 94-8862 in Rats)

Sex	Males					Females				
Dose (mg/kg/day)	0	0	2	6	20	0	0	1	3	10
Total number of animals on study	60	60	60	60	60	60	60	60	60	60
Total number of decedent animals	21	19	17	27	20	19	17	18	16	17
Total number at terminal kill	39	41	43	33	40	41	43	42	44	43

Source: Applicant's table

Figure 20. Summary of Survival Data in Males (Study BAY 94-8862 in Rats)

Figure 8.1: Summary of Survival Data – Males

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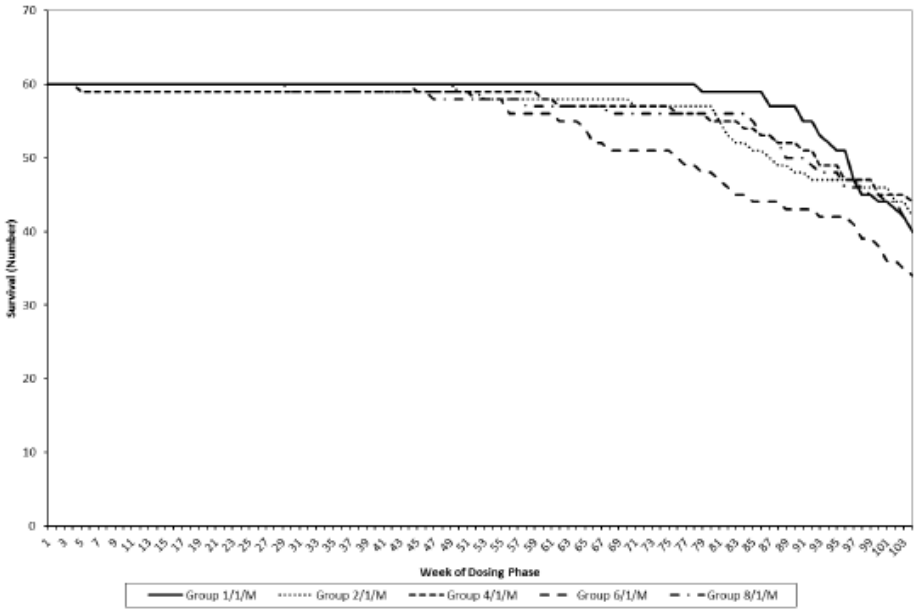
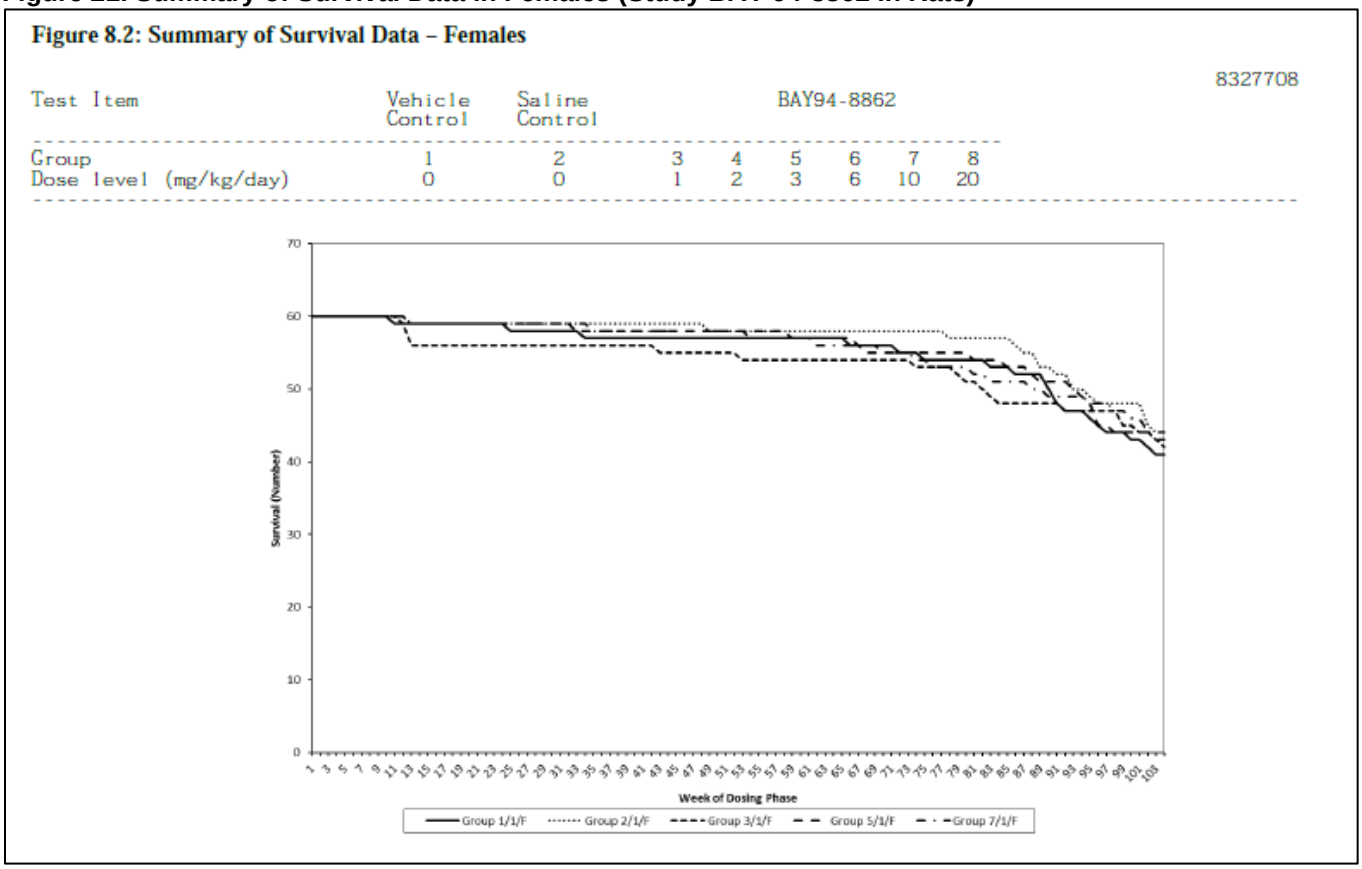
Test Item	Vehicle Control	Saline Control	BAY94-8862					
Group	1	2	3	4	5	6	7	8
Dose level (mg/kg/day)	0	0	1	2	3	6	10	20



Source: Applicant's figure

Figure 21. Summary of Survival Data in Females (Study BAY 94-8862 in Rats)



Source: Applicant's figure

Clinical Signs

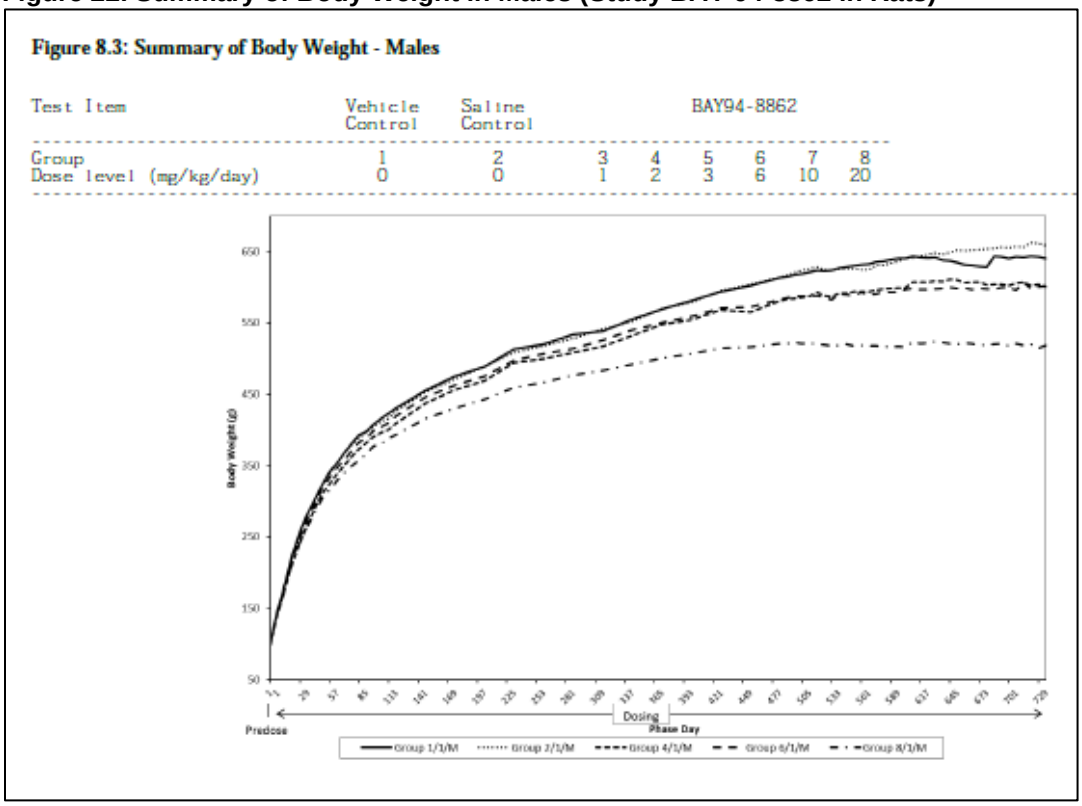
A BAY 94-8862-related clinical observation included thin appearance for males administered 20 mg/kg/day. Slightly higher incidence of thin appearance for males administered 20 mg/kg/day, compared with controls, correlated with decreased body weight gain and reduced food consumption in these animals. Therefore, thin appearance was considered test item-related.

Body Weights

Administration of BAY 94-8862 resulted in minimally to markedly lower mean body gain for males administered 20 mg/kg/day and minimally lower mean body weight gain for females administered 10 mg/kg/day (Figure 22 and Figure 23).

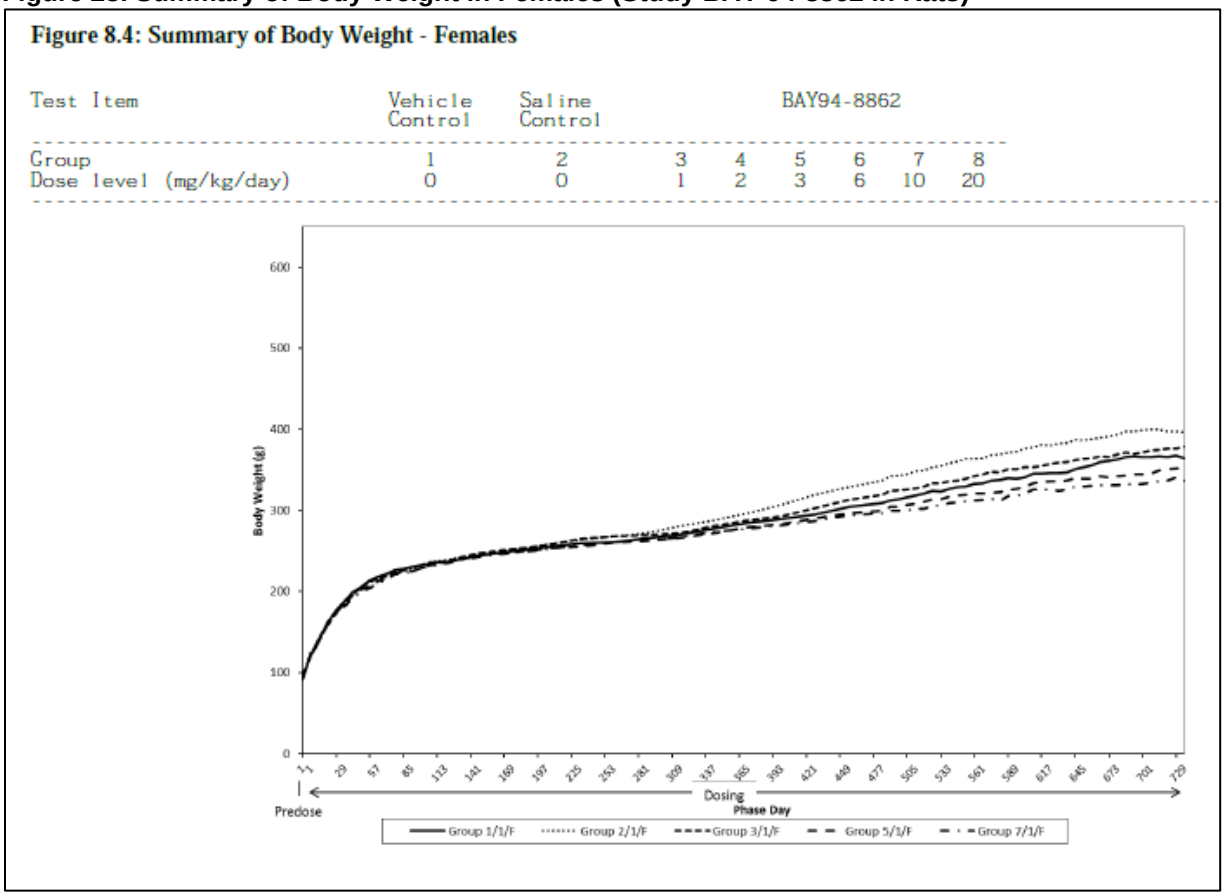
Minimally to markedly lower mean body gain was noted throughout the dosing phase for males administered 20 mg/kg/day, compared with the vehicle control group, such that mean body weight at the end of dosing phase and overall mean body weight gain (Days 1 to 729) were 19 and 24% lower, respectively, than the vehicle control group. Occasionally, lower mean body weight gain was noted for females administered 10 mg/kg/day, but the trend was not consistent. Mean body weight at the end of dosing phase and overall mean body weight gain (Days 1 to 729) was 8 and 12% lower, respectively, than the vehicle control group.

Figure 22. Summary of Body Weight in Males (Study BAY 94-8862 in Rats)



Source: Applicant's figure

Figure 23. Summary of Body Weight in Females (Study BAY 94-8862 in Rats)



Source: Applicant's figure

Feed Consumption

Administration of BAY 94-8862 resulted in minimally lower mean food consumption throughout the dosing phase for males administered 20 mg/kg/day, compared with the vehicle control group, such that overall mean food consumption (Days 1 to 729) was 8% lower than the vehicle control group. These decreases in food consumption correlated with decreased body weight gain and were considered test item related.

Gross Pathology

No macroscopic findings considered to be BAY 94-8862-related were noted for test item-treated decedents as tissues were macroscopically unremarkable or the findings observed were generally consistent with the usual pattern of findings in rats of this strain and age.

Histopathology

Peer Review Conducted: Yes

Historical Control Provided for Tumor Incidence: Yes

Carcinogenicity animals were weighed before necropsy. Organs denoted by *W* in the following tissue list from all carcinogenicity animals were dissected free from fat and other contiguous tissue and weighed before fixation. Left and right organs were weighed together.

A full macroscopic examination was performed for each necropsied animal under the general supervision of a Pathologist, and all lesions were recorded. The following tissues from each necropsied animal were preserved in 10% neutral-buffered formalin, unless otherwise indicated (Table 81).

Tissues Examined

Table 81. List of Tissues Undergoing Histopathology Evaluation (Study BAY 94-8862 in Rats)

Organ/Tissue			Organ/Tissue		
adrenal	W	E	nerve, sciatic		E
animal identification			nose/nares		
aorta		E	ovary	W	E
bone marrow smear (femur)[a,b]			oviduct		E
brain	W	E	pancreas		E
cecum (transverse section)		E	parotid salivary gland		E
colon		E	pituitary		E
duodenum		E	preputial/clitoral gland		E
epididymis (longitudinal sections)[c]	W	E	prostate		E
esophagus		E	rectum		E
eye[d]		E	seminal vesicle including coagulating glands		E
femur with bone marrow and femorotibial joint		E	skin and subcutis		E
gut-associated lymphoid tissue (GALT)/Peyer's patch			spinal cord, cervical		E
gross lesions		E	spinal cord, lumbar		E
Harderian gland		E	spinal cord, thoracic		E
Head (not processed)			spleen	W	E
Heart	W	E	sternum with bone marrow		E
Ileum		E	stomach (forestomach and glandular stomach)	W	E
Jejunum		E	sublingual salivary gland		E
kidney (transverse and longitudinal section)	W	E	testis (longitudinal sections)[c]	W	E
lacrimal gland		E	thymus		E
larynx		E	thyroid with parathyroid		E
liver	W	E	tissue masses		E
lungs with main stem bronchi and bronchioles		E	tongue		E
lymph node, iliac			trachea		E
lymph node, mandibular		E	ureter		E
lymph node, mesenteric		E	urethra		
mammary gland		E	urinary bladder		E
mandibular salivary gland		E	uterus with cervix[f]	W	E
mesentery		E	vagina		E
muscle, quadriceps		E	Zymbal's gland		E

Organ/Tissue		Organ/Tissue
nasal cavity[e]	E	
nasopharynx		
nerve, optic	E	

E = Processed and examined microscopically; W = Weighed.
Note: Bone designated for microscopic examination was decalcified using Kristenson's fluid.
a Methanol fixative.
b See Section 3.5.2.
c Tissue taken into Modified Davidsons fixative and processed to at least the block stage and weighed separately.
d Davidson's fixative.
e Level 1 and 4.
f Horns transverse section, longitudinal cut from the cervix including horn parts.

Source: Applicant's table

Neoplastic

No neoplastic findings considered BAY 94-8862-related were noted by the sponsor on this study and no statistically significant increase in neoplastic lesions was noted for either sex administered BAY 94-8862. This is consistent with the FDA statistical reviewer's analysis and conclusion (Table 82).

Based on this, the NOAELs are concluded to be 20 mg/kg/day in males and 10 mg/kg/day in females.

Table 82. Summary Table of Tumor Types With P-Values ≤0.05 for Dose-Response-Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle Control Group in Study BAY 94-8862 in Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Male						
Thyroid	B-Follicular Cell Adenoma	2/60 (56)	3/60 (53)	0/60 (48)	6/60 (53)	1/60 (53)
		0.0343 @	0.4737	1.0000	0.1181	0.8680
	M-Follicular Cell Carcinoma	0/60 (56)	1/60 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.3067	0.4862	NC	0.4862	NC
	B-Follicular Cell Adenoma/ M-Follicular Cell Carcinoma	2/60 (56)	4/60 (53)	0/60 (48)	7/60 (53)	1/60 (53)
		0.0245 @	0.3134	1.000s0	0.0684	0.8680
		0 mg	1 mg	3 mg	10 mg	0 mg
Female						
Mammary Gland	B-Fibroadenoma	4/58 (50) &	7/59 (51)	3/59 (53)	7/57 (51)	14/59 (54)
		0.2413	0.2740	0.8051	0.2740	0.0142 @
Pituitary	B-Adenoma, Pars Distalis	29/60 (55)	34/60 (53)	25/60 (56)	27/60 (56)	40/60 (57)
		0.8461	0.1566	0.8513	0.7470	0.0440 @
	B-Adenoma, Pars Intermedia	0/60 (52)	1/60 (50)	0/60 (52)	1/60 (52)	1/60 (54)
		0.3140	0.4902	NC	0.5000	0.5094
	B-Adenoma, Pars Distalis/ B-Adenoma, Pars Intermedia	29/60 (55)	35/60 (53)	25/60 (56)	28/60 (56)	41/60 (57)
		0.8125	0.1128	0.8513	0.6833	0.0282 @
Thyroid	B-C-Cell Adenoma	2/60 (52)	2/60 (50)	7/60 (52)	8/60 (52)	4/60 (54)
		0.0183 @	0.6763	0.0801	0.0462 @	0.3574
	M-C-Cell Carcinoma	0/60 (52)	0/60 (50)	1/60 (52)	0/60 (52)	0/60 (54)
		0.5049	NC	0.5000	NC	NC
	B-C-Cell Adenoma/ M-C-Cell Carcinoma	2/60 (52)	2/60 (50)	8/60 (52)	8/60 (52)	4/60 (54)
		0.0217 @	0.6763	0.0462 @	0.0462 @	0.3574

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.
@ = Not statistically significant in common tumor at 0.005 level for test of dose response relationship or at 0.01 level for test of pairwise comparisons;

Source: Statistical reviewer's table

Non-Neoplastic

Upon microscopic examination, BAY 94-8862-related, statistically significant, hypertrophic/hyperplastic findings were recorded for the adrenal gland (Table 83). In the adrenal gland, statistically significant (P-value=0.001), slight-to-severe, diffuse, zona glomerulosa hypertrophy was noted in most animals administered 1, 2, 3, 6, 10, or 20 mg/kg/day BAY 94-8862 and two female controls. This was characterized by an increase in the amount of cytoplasm of the cortical cells within this region with an overall increase in the thickness of the zona glomerulosa and generally correlated with the macroscopic finding of pale adrenal glands. A corresponding statistically significant decrease (P-value=0.001 for males; P-value 0.280 for females administered 1 mg/kg/day and P-value=0.001 for all other treated females) in focal (to multifocal) hypertrophy of the zona glomerulosa was noted in both sexes in all BAY 94-8862-treated groups. Focal zona glomerulosa hypertrophy was characterized by small aggregates composed of increased numbers of variably enlarged cortical cells with pale cytoplasm within this region.

A statistically significant (P-value 0.007) increase in focal medullary hyperplasia was noted in males administered 20 mg/kg/day, compared with vehicle and saline controls. Medullary hyperplasia was characterized by small, focal areas of increased numbers of small medullary cells with increased cytoplasmic basophilia, but without distortion/compression of the adjacent adrenal medulla.

These effects are consistent with the findings from the 6-month repeat-dose toxicity study in rats and are attributed to the pharmacological activity of BAY 94-8862.

Table 83. Adrenal Gland Histopathology Summary (Study BAY 94-8862 in Rats)

		Males					Females				
		1M	2M	4M	6M	8M	1F	2F	3F	5F	7F
Tissue and finding	Level (mg/kg/day)	0	0	2	6	20	0	0	1	3	10
Adrenal gland	No. examined:	60	60	60	60	60	60	60	60	60	60
hypertrophy, diffuse zona glomerulosa	Grade -	60	60	14	0	0	59	59	30	9	2
	1	0	0	0	0	0	0	0	0	0	0
	2	0	0	40	22	0	1	0	28	35	9
	3	0	0	6	29	14	0	0	1	16	27
	4	0	0	0	9	25	0	1	1	0	20
	5	0	0	0	0	21	0	0	0	0	2
hypertrophy, focal, zona glomerulosa	Grade -	23	28	47	56	57	24	19	37	49	52
	1	37	31	13	1	1	34	40	22	10	5
	2	0	1	0	3	1	2	1	1	1	3
	3	0	0	0	0	1	0	0	0	0	0
hyperplasia, medulla - focal	Grade -	53	52	51	47	36	57	58	58	59	60
	1	2	5	4	10	12	1	2	1	1	0
	2	2	3	4	2	8	2	0	0	0	0
	3	2	0	1	1	4	0	0	1	0	0
	4	1	0	0	0	0	0	0	0	0	0

- = Finding not present; 1 = Minimal; 2 = Slight; 3 = Moderate; 4 = Marked; 5 = Severe; F = Female; M = Male.

Source: Applicant's table

Other notable non-neoplasm tissue changed included enhanced vacuolation of adrenal cortical cells (z. glomerulosa) as well as increased cortico-medullary pigmentation in the adrenals and the spleen.

Toxicokinetics

The exposure of the test item in terms of dose-normalized AUC from 0 to 24h ($AUC_{0-24norm}$) and dose-normalized C_{max} ($C_{max,norm}$) were considerably higher (2.3- to 3.8-fold) in females, compared with males. On Day 361, the exposure (AUC_{0-24} and C_{max}) of the parent compound increased dose-proportionally from 1 to 3 mg/kg/dose for females and 2 to 6 mg/kg/day for males and slightly to moderately less-than-dose proportional from 3 to 10 mg/kg/day for females and 6 to 20 mg/kg/day for males (Table 84).

The exposure of the parent compound in terms of AUC_{0-24} and C_{max} was considerably higher after multiple doses (Day 361), especially in females (females 2.2- to 4.6-fold; males 1.7- to 3.9-fold), compared with Day 1 (Table 83). The relative exposure of the metabolites (AUC_{0-24}) was very low (<1% of the exposure of the parent compound) after multiple doses (Day 361).

Males Day 361:

Table 84. Toxicokinetics of Parent Compound BAY 94-8862 at Day 1 and Day 361 in Males (Study BAY 94-8862 in Rats)

Male, Day 1

Dose Time [h]	[mg/kg]	2 gMean [µg/L]	gSD	6 gMean [µg/L]	gSD	20 gMean [µg/L]	gSD
0.5		3190	1.18	10900	1.20	43300	1.17
1		4290	1.18	12900	1.29	42500	1.25
2		6220	1.19	14700	1.25	43700	1.68
4		7860	1.04	23500	1.05	70500	1.22
7		9230	1.02	12500	4.48	83500	1.09
24		2400	1.53	5420	1.83	18100	1.25

Parameter	Unit			
AUC(0-tlast)	µg·h/L	134000	257000	1150000
AUC(0-tlast)norm	kg·h/L	66.9	42.9	57.4
tlast	h	24.0	24.0	24.0
Cmax	µg/L	9230	23500	83500
Cmax,norm	kg/L	4.61	3.92	4.18
tmax	h	7.00	4.00	7.00
C(tint)/Cmax	%	26.0	23.1	21.6
t(int)	h	24.0	24.0	24.0

Male, Day 361

Dose Time [h]	[mg/kg]	2 gMean [µg/L]	gSD	6 gMean [µg/L]	gSD	20 gMean [µg/L]	gSD
0.5		15100	1.35	47300	1.24	115000	1.26
1		17400	1.26	61300	1.06	118000	1.09
2		17100	1.30	46700	1.53	130000	1.01
4		16000	1.28	51600	1.13	125000	1.24
7		17400	1.02	64700	1.10	143000	1.04
24		7630	1.49	21100	1.91	60200	1.04

Parameter	Unit			
AUC(0-tlast)	µg·h/L	314000	1030000	2490000
AUC(0-tlast)norm	kg·h/L	157	171	125
tlast	h	24.0	24.0	24.0
Cmax	µg/L	17400	64700	143000
Cmax,norm	kg/L	8.71	10.8	7.14
tmax	h	7.00	7.00	7.00
C(tint)/Cmax	%	43.8	32.6	42.1
t(int)	h	24.0	24.0	24.0
RA-AUC(0-tlast)	%	234.5	398.7	217.1
RA-Cmax	%	188.8	275.1	171.1

Source: Applicant's table
Abbreviations: AUC, area under the curve; RA-AUC, ratio of accumulation for AUC ((AUC on Day 361)/(AUC on Day 1) *100))

Table 85. Toxicokinetics of Parent Compound BAY 94-8862 at Day 1 and Day 361 in Females (Study BAY 94-8862 in Rats)

Female, Day 1

Dose [mg/kg]	1		3		10	
Time [h]	gMean [µg/L]	gSD	gMean [µg/L]	gSD	gMean [µg/L]	gSD
0.5	2120	1.21	8840	1.17	26900	1.34
1	2230	1.12	9750	1.15	27500	1.23
2	2540	1.51	9190	1.29	32700	1.41
4	5300	1.06	16200	1.24	54800	1.23
7	6500	1.09	23500	1.07	72600	1.08
24	5370	1.24	20500	1.05	52100	1.25

Parameter	Unit			
AUC(0-tlast)	µg·h/L	130000	475000	1380000
AUC(0-tlast)norm	kg·h/L	130	158	138
tlast	h	24.0	24.0	24.0
Cmax	µg/L	6500	23500	72600
Cmax,norm	kg/L	6.50	7.84	7.26
tmax	h	7.00	7.00	7.00
C(tint)/Cmax	%	82.7	87.1	71.8
t(int)	h	24.0	24.0	24.0

Female, Day 361

Dose [mg/kg]	1		3		10	
Time [h]	gMean [µg/L]	gSD	gMean [µg/L]	gSD	gMean [µg/L]	gSD
0.5	29200	1.13	80600	1.10	144000	1.03
1	25700	1.15	65200	1.05	160000	1.15
2	25900	1.24	94700	1.11	144000	1.08
4	29500	1.14	78300	1.05	158000	1.06
7	28400	1.10	73500	1.06	163000	1.05
24	20400	1.14	79300	1.18	110000	1.07

Parameter	Unit			
AUC(0-tlast)	µg·h/L	599000	1840000	3340000
AUC(0-tlast)norm	kg·h/L	599	612	334
tlast	h	24.0	24.0	24.0
Cmax	µg/L	29500	94700	163000
Cmax,norm	kg/L	29.5	31.6	16.3
tmax	h	4.00	2.00	7.00
C(tint)/Cmax	%	69.1	83.7	67.7
t(int)	h	24.0	24.0	24.0
RA-AUC(0-tlast)	%	460.5	386.4	242.1
RA-Cmax	%	453.6	402.5	224.4

Source: Applicant's table
Abbreviations: AUC, area under the curve; RA-AUC, ratio of accumulation for AUC ((AUC on Day 361)/(AUC on Day 1) *100)

14. Clinical Pharmacology: Additional Information and Assessment

14.1. In Vitro Studies

Finerenone, known as BAY94-8862, is metabolized to several metabolites. The two major biotransformation pathways are oxidation of the dihydronaphthyridine to the naphthyridine derivative M-1, followed by hydroxylation, leading to the hydroxymethyl naphthyridine metabolite M-2 with subsequent oxidation leading to the carboxylic acid M-3. There is presumably an intermediate epoxidation with subsequent hydrolysis leading to the dihydrodiol M-4 and further hydroxylation to M-5. The predominant human plasma metabolites M-1, M-2, and M-3 have axial chirality and therefore form atropisomers M-1a, M-1b, M-2a, M-2b, M-3a, and M-3b. M-1a, M-1b, M-2a, and M-3a are major human plasma metabolites, and each account for >10% of the AUC of total drug related components. Finerenone and its metabolites were evaluated in several in vitro studies.

14.1.1. Plasma Protein Binding (A44959, A50452, PH-38807, PH-38806, PH-38807, A60708)

Binding of finerenone to plasma proteins was moderate in humans, with the fraction unbound in humans at 8.33% determined in vitro with concentrations in the clinically relevant range (concentration range tested: 94.5 to 4289 µg/L). The blood/plasma ratio in human whole blood was 0.935 when tested at these concentrations; however, when increased to 83087 µg/L, the ratio increased to 1.09. There was saturation of plasma protein binding with a slight increase of the unbound finerenone fraction observed at the highest tested total concentration of 87549 µg/L. The majority of finerenone bound to albumin in human plasma. In vitro, when tested at a concentration of 5287 µg/L with human serum albumin, the fraction unbound was 16.5%. Finerenone also bound to α1-acidic glycoprotein, LDL, and γ-globulins. In vitro, when tested at a concentration of 4934 µg/L with α1-acidic glycoprotein, the fraction unbound was 59.3%. In vitro, when tested at a concentration of 4988 µg/L with α-globulins, the fraction unbound was 58.9%. In vitro, when tested at a concentration of 4948 µg/L with γ-globulins, the fraction unbound was 84.4%. In vitro, when tested at a concentration of 4984 µg/L with LDL, the fraction unbound was 59.8%. Albumin, α1-acidic glycoprotein, α-globulins, γ-globulins, and LDL were tested at concentrations of 600, 23, 80, 66.2, and 1 µM, respectively.

In vitro binding investigations were also completed for finerenone metabolites BAY 1117267 (M-1a), BAY 1117268 (M-2a), and BAY 1117271 (M-3a). Plasma protein binding was quite low in humans at all concentrations tested (35.1 to 3408 µg/L) for M-3a, with a mean unbound fraction of 67.8%. Metabolite M-2a was more highly bound at all concentrations tested (48.6 to 4297 µg/L), with a mean unbound fraction of 17.4%. Metabolite M-1a was the metabolite with the most protein binding at the concentrations tested (45.9 to 4398 µg/L), with a mean unbound fraction of 5.82. The binding for each metabolite was similar across all concentrations tested. The plasma/blood ratios were tested at three concentrations in the range between 25.9 and 4602 µg/L [^{3}H]-metabolites. The average ratios for M-1a, M-2a, and M-3a were 164, 140, and 133, respectively. These ratios were similar across all concentrations tested. Binding investigations were also conducted for metabolite M-1b (BAY 1117266) using [^{14}C]BAY 1117266, tested at concentrations ranging from 37 to 4620 µg/L. The unbound fraction in humans was 3.88%.

Binding to human liver microsomes was assessed, and unbound fractions were determined by ultrafiltration using [^{14}C]finerenone. Concentrations ranging from approximately 1 µM to 20 µM were tested in human liver microsomes. In human liver microsomes at 0.05, 0.1, and 0.5 mg/mL, the unbound fractions ranged between 86.3 to 87.2%, 80.7 to 81.3%, and 59 to 62.1%, respectively, indicating that the protein binding to human liver microsomes is dependent on microsomal concentration in the assay, not finerenone concentration.

Binding to human liver microsomes was also assessed for metabolites BAY 1117267 (M-1a), BAY 1117266 (M-1b), BAY 1117268 (M-2a) and BAY 1117271 (M-3a). The concentrations tested were 571 to 14901 µg/L, 340 to 7044 µg/L, 481 to 11607 µg/L, and 356 to 7838 µg/L for M-1a, M-1b, M-2a, and M-3a, respectively. For M-1a, the mean unbound fraction was 91.1%, 84.8%, and 66.2% for human liver microsomes at 0.05, 0.1, and 0.5 mg/mL, respectively. For M-1b, the mean unbound fraction was 89.1%, 84.2%, and 58% for human liver microsomes at 0.05, 0.1, and 0.5 mg/mL, respectively. For M-2a, the mean unbound fraction was 92.9%, 91.5%, and 82.8% for human liver microsomes at 0.05, 0.1, and 0.5 mg/mL, respectively. For M-3a, the mean unbound fraction was 93.4%, 92.8%, and 83.8% for human liver microsomes at 0.05, 0.1, and 0.5 mg/mL, respectively. Change in binding between test article concentrations was minimal except for M-3a in human liver microsomes at 0.5 mg/mL. In human liver microsomes at 0.5 mg/mL, an M-3a concentration of 387 µg/L was 84.4% unbound, and an M-3a concentration of 7838 µg/L was 83.3% unbound.

In humans, oxidative metabolism of finerenone leads to the formation of three major metabolites, M-1 (BAY 1040818), M-2 (BAY 1088089) and M-3 (BAY 1088090). Of all three metabolites, two different atropisomers are formed, named a- and b-isomer for each metabolite. Although the a-atropisomers are formed to a much higher extent than the b-isomers, it cannot be ruled out that the protein binding of the a-isomers differs to some extent of that of the mixture of a- and b-isomer as it is found in plasma. To determine the fraction unbound of the atropisomer mixtures, plasma was obtained from healthy subjects and renally impaired patients after administration of finerenone in Study 14509. The concentration of each isomer mixture was determined by HPLC-MS/MS analysis without chiral chromatographic separation. In a second experiment, radioactively labeled a-atropisomers were spiked in aliquots of the same plasma samples to determine the unbound fraction of the a-isomers alone via ultrafiltration and liquid scintillation counting. For the metabolite M-1 (BAY 1040818) the mean unbound fraction was 5.64% (range: 3.76 to 9.00%), for M-2 (BAY 1088089) the mean unbound fraction was 14.7% (range: 9.80 to 23.1%), and for M-3 (BAY 1088090) the mean unbound fraction amounted to 83.1% (range: 62.6 to 122%). For M-1a (BAY 1117267) the mean unbound fraction was 7.08% (range: 3.79 to 11.3%). M-2a (BAY 1117268) had a mean unbound fraction of 19.0% (range: 13.4 to 29.4%). M-3a (BAY 1117271) had a mean unbound fraction that of 80.6% (range: 74.7 to 85.0%). Therefore, the extent of protein binding of the a-atropisomer series and the isomer mixtures is not different within experimental variability and the range of the determined unbound fractions.

14.1.2. Metabolism Studies

Report PH-41146 discussed metabolite profiling in human liver microsomes and hepatocytes. In human liver microsomes, there was evidence of M-5, M-4, M-7, M-2/M-6, M-3, and M-1 metabolites, as well as traces of the M-14 metabolite. In hepatocytes, M-5, M-4, M-7, M-2/M-6, and M-1 were present. Atropisomer ratios in in vitro incubations of finerenone at 1 µM in pooled

human liver microsomes show 94.6% M-1a, 5.41% M-1b, 96.2% M-2a, and 3.83% M-2b. M-3a and M-3b were not detected in this assay in human liver microsomes.

Report PH-39534 examined in vitro identification of human CYP isoforms involved in the metabolism of finerenone. Five CYP isoforms, mostly CYP3A4 and to a lesser extent CYP1A1, CYP2C8, CYP3A5, and CYP3A7, were able to metabolize finerenone and formed metabolites from both the naphthyridine (M-1, M-2, and M-3) and the dihydrodiol pathways (M-4, M-5). CYP2C8 formed M-7 and the CYP1A1 specific metabolite M-13 was also formed. Table 86 shows the mass balance of 1 µM incubates with CYP isoforms, and Table 87 shows clearance and metabolite formation in CYP1A1, 2C8, 3A4, and human liver microsomes. Clearance and calculated hepatic fraction metabolized in 0.2 µM incubates with human hepatocytes and CYP3A4/2C8 selective inhibitors are shown in Table 88. Pathway contribution in 0.2 µM incubates with human hepatocytes and CYP3A4/2C8 selective inhibitors are shown in Table 89. Atropisomer formation in 50nM incubates with CYP1A1, 2C8, 3A4, and human liver microsomes are reported in Table 90.

Table 86. [14C]Finerenone Mass Balance of 1 µM Incubates With CYP Isoforms

Incubation RMA1487	CYP Isoform	[^{14}C]Finerenone [%]	M1 [%]	M2[a] [%]	M2 + M6[a] [%]	M3 [%]	M4 [%]	M5 [%]	M6[a] [%]	M7 [%]	M11 [%]	M12 [%]	M13 [%]	M14 [%]
B21	Insect cell Ctr	99.5	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B01	1A1	65.0	5.2	NA	3.5	ND	3.9	ND	NA	1.6	ND	ND	19.6	ND
B02	1A2	98.1	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B03	2A6	97.0	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B04	2B6	97.4	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B05	2C8	23.0	19.4	ND	NA	ND	24.5	ND	3.9	5.5	13.7	1.0	ND	6.7
B06	2C9	99.0	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B07	2C18	96.1	<2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B08	2C19	96.3	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B09	2D6	97.2	<2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B10	2E1	97.4	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B11	2J2	97.7	<2	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B12	3A4	7.6	9.7	37.1	NA	1.1	14.2	20.2	<1	ND	ND	ND	ND	3.5
C04	3A5	85.5	4.1	NA	1.3	ND	5.7	1.0	NA	1.0	ND	ND	ND	0.5
C05	3A7	86.9	6.6	NA	1.2	ND	4.9	ND	NA	ND	ND	ND	ND	0.5
B16	4A11	98.5	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B17	4F2	99.3	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B18	4F3A	98.2	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B19	4F3B	99.0	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
B20	4F12	99.4	<1	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

Source: Applicant, Studies KINM 090030-ELB KINM 120157-ELB, Report PH-39534, Table 6-2.
[a]insufficient chromatographic separation of M-2 and M-6 – depending on their occurrence in MS, they are balanced separately or together
Abbreviations: Ctr, control; NA, not applicable; ND, not detected

Table 87. Clearance and Metabolite Formation in 50nM Incubates With CYP1A1, 2C8, 3A4, and Human Liver Microsomes

Time [min]	Finerenone [%]	CL_{int}	M1	M2	M3	M4	M5	M7	M13
			[MS response]						
CYP1A1 100 pmol/mL (LAND0607K01)									
0	100.0		ND	ND	ND	ND	ND	ND	ND
6	90.4		2245	ND	ND	15368	ND	ND	44685
10	82.1	0.22	15127	ND	ND	18258	ND	ND	75153
15	73.1	µL/min/pmol	17558	ND	ND	19567	ND	ND	108277
25	62.1		20099	5223	ND	32292	ND	5374	158466
45	49.0		27497	5489	ND	46192	ND	8120	225801
CYP2C8 100 pmol/mL (LAND0607K05)									
0	100		ND	ND	ND	ND	ND	ND	ND
6	97.2		3095	ND	ND	94534	ND	ND	ND
10	89.9	0.12	23983	ND	ND	155661	ND	ND	ND
15	82.0	µL/min/pmol	45440	ND	ND	220092	ND	ND	ND
25	72.0		97967	ND	ND	324382	ND	8855	ND
45	55.8		142209	ND	ND	489685	ND	8141	ND
CYP3A4 75 pmol/mL (LAND0607K09)									
0	100		ND	ND	ND	ND	ND	ND	ND
6	40.7		471477	212425	ND	264971	128121	ND	ND
10	22.3	1.91	456503	404322	ND	334647	153460	ND	ND
15	11.1	µL/min/pmol	323734	563419	ND	347500	199526	ND	ND
25	1.5		161595	639213	31589	290294	225092	ND	ND
45	0.2		28907	594262	115054	186778	248024	ND	ND
HLM 0.5 mg/mL (LAND0607Q01)									
0	100.0		ND	ND	ND	ND	ND	ND	ND
5	92.1		86308	ND	ND	52423	ND	ND	ND
10	83.2	38.83	164771	ND	ND	114502	4740	ND	ND
15	75.4	µL/min/mg	264012	ND	ND	169739	23318	ND	ND
25	64.1		373499	6208	ND	222275	41159	ND	ND
45	40.7		484183	59056	ND	330524	65860	ND	ND

Source: Applicant, Studies KINM 090030-ELB KINM 120157-ELB, Report PH-39534, Table 6-3.
Abbreviations: CL, clearance; ND, not detected

Table 88. Finerenone Clearance and Calculated Hepatic Fraction Metabolized (fm) in 0.2 µM Incubates With Human Hepatocytes and CYP3A4/2C8 Selective Inhibitors

	CL_{int}	Inhibition	Calculated hepatic f_m	
	[L/h/kg]	[%]	CYP3A4	CYP2C8
w/o inhibitor	2.33	-		
Gemfibrozil	1.29	45	0.55	0.45
Verapamil	0.30	87	0.87	0.13
Verapamil + Gemfibrozil	0.01	100		
Erythromycin	0.53	77	0.79	0.21
Erythromycin + Gemfibrozil	0.07	97		

Source: Applicant, Studies KINM 090030-ELB KINM 120157-ELB, Report PH-39534, Table 6-5.
Abbreviations: CL, clearance

Table 89. Pathway Contribution in 0.2 µM Incubates With Human Hepatocytes and CYP3A4/2C8 Selective Inhibitors

	iMSR	Inhibition	Calculated pathway contribution	
	[MS response·min]	[%]	CYP3A4	CYP2C8
Naphthyridine pathway (Sum of M1, M2, M3)				
w/o inhibitor	150409860			
Gemfibrozil	162739650	-8.2	1.1	-0.1
Verapamil	27566190	81.7	0.9	0.1
Verapamil + Gemfibrozil	15967170	89.4		
Erythromycin	45175110	70.0	0.8	0.2
Erythromycin + Gemfibrozil	14970090	90.0		
Dihydrodiol pathway (Sum of M4, M5, M11)				
w/o inhibitor	372587940			
Gemfibrozil	249039675	33.2	0.6	0.4
Verapamil	228691005	38.6	0.4	0.6
Verapamil + Gemfibrozil	41644485	88.8		
Erythromycin	393937245	-5.7	-0.1	1.1
Erythromycin + Gemfibrozil	40425030	89.2		
Methyl hydroxylation pathway (Sum of M2, M5, M7)				
w/o inhibitor	118225650			
Gemfibrozil	97500855	17.5	0.8	0.2
Verapamil	8787375	92.6	0.9	0.1
Verapamil + Gemfibrozil	856770	99.3		
Erythromycin	18738900	84.1	0.9	0.1
Erythromycin + Gemfibrozil	1426065	98.8		

Source: Applicant, Studies KINM 090030-ELB KINM 120157-ELB, Report PH-39534, Table 6-6.

Table 90. Finerenone Atropisomer Formation in 50nM Incubates With CYP1A1, 2C8, 3A4, and Human Liver Microsomes

Incubation LAND0607	Enzyme	M1a [nM]	M1b [nM]	M1a [%]	M1b [%]	M2a [nM]	M2b [nM]	M2a [%]	M2b [%]
K01[a]	CYP1A1	0.85	0.43	67	33	0.2	0.9	16	84
K05[a]	CYP2C8	2.19	0.91	71	29	ND	ND	NA	NA
K09[b]	CYP3A4	8.22	0.37	96	4	9.0	0.2	98	2
Q01[a]	HLM	8.49	0.41	95	5	2.64	0.10	96	4

Source: Applicant, Studies KINM 090030-ELB KINM 120157-ELB, Report PH-39534, Table 6-8.
[a] determined after 45 min
[b] determined after 10 min due to nonlinearity of M1 formation
Abbreviations: NA, not applicable; ND, not detected

In conclusion, CYP3A4 was the most relevant enzyme in the biotransformation of finerenone, followed by CYP2C8. The hepatic fraction metabolized by CYP3A4 is estimated to be ≥80%, which was confirmed in dedicated clinical DDI studies. By using CYP3A4-specific inhibitors erythromycin and verapamil, as well as CYP2C8-specific inhibitor gemfibrozil-glucuronide, a hepatic fraction metabolized via CYP3A4 of 80 to 90% was calculated. The remainder could be assigned to CYP2C8. Contributions of CYP1A1 to finerenone metabolism were considered irrelevant by the Applicant. M-1a and M-2a were the dominant isomers of M-1 and M-2. When

incubated with CYP3A4 and human liver microsomes, the a-atropisomer was formed preferentially (>95%).

CYP3A4 showed the highest clearance with 1.91 µL/min/pmol, followed by CYP1A1 and CYP2C8 with 0.22 and 0.12 µL/min/pmol, respectively, demonstrating that CYP3A4 was the most efficient in metabolizing finerenone.

In Study PH-37733, finerenone showed inhibition of CYP2C8, CYP2C9, and CYP2C19. Finerenone was able to reversibly inhibit CYP2C8 and CYP3C9, with K_i values of 1.9 and 16 µM, respectively. There was reversible and irreversible inhibition on CYP3A4. There was also evidence for time-dependent inhibition for CYP3A4. Studies PH-37685 and PH-40973 also looked at finerenone and metabolite inhibition. Table 91 shows CYP isozymes for which a test article (either finerenone, M-1a, M-1b, M-2a, M-2b, M-3a, or M-3b) resulted in a calculable IC_{50} value for inhibition.

Table 91. *In Vitro* Assessments of Finerenone and Metabolites as Inhibitors of CYPs (Study PH-37733, Study PH-37685, PH-40973)

Isozyme Test Article	Activity	Inhibitor Positive Control (IC_{50} µM)	IC_{50} for Finerenone (µM)	Conclusion	Study Report	System
CYP2C8						
Finerenone	Amodiaquine deethylation	Quercetin (0.71 µM)	6.8	Inhibition of CYP2C8	PH-37733	Human liver microsomes
CYP2C9						
Finerenone	Diclofenac 4'-hydroxylation	Sulfaphenazole (0.31 µM)	29	Inhibition of CYP2C9	PH-37733	Human liver microsomes
M-1a		Sulfaphenazole (0.04 µM)	25		PH-37685	
CYP2C19						
Finerenone	(S)-mephenytoin 4'-hydroxylation	(-)-N-3-Benzylpheno-barbital (0.88 µM)	31	Inhibition of CYP2C19	PH-37733	Human liver microsomes
CYP3A4						
Finerenone	Testosterone 6β-hydroxylation	Ketoconazole (0.04 µM)	19	Inhibitor of CYP3A4	PH-37733	Human liver microsomes
CYP3A4 – metabolism dependent						
Finerenone	Testosterone 6β-hydroxylation	Mibefradil (0.07 µM)	10	Inhibitor of CYP3A4	PH-37733	Human liver microsomes
CYP3A4						
Finerenone	Midazolam 1'-hydroxylation	Ketoconazole (0.04 µM)	12	Inhibitor of CYP3A4	PH-37733	Human liver microsomes
CYP3A4 – metabolism dependent						
Finerenone	[$^{13}C_6$]Midazolam 1'-hydroxylation	Mibefradil (0.08 µM)	6.4	Inhibitor of CYP3A4	PH-37733	Human liver microsomes
CYP1A1						
Finerenone M-1a M1-b	Granisetron 7-hydroxylation	7-hydroxyflavone (0.0091 µM)	6.7 30 29	Inhibitor	PH-40973	Recombinant CYP 1A1
CYP1A1 (pre-incubation -NADPH)						
Finerenone M-1a M1-b	Granisetron 7-hydroxylation	Erlotinib (0.014 µM)	9.5 35 32	Metabolism-dependent inhibition	PH-40973	Recombinant CYP 1A1

Isozyme Test Article	Activity	Inhibitor Positive Control (IC_{50} µM)	IC_{50} for Finerenone (µM)	Conclusion	Study Report	System
CYP1A1 (pre-incubation +NADPH)						
Finerenone M-1a M1-b	Granisetron 7-hydroxylation	Erlotinib (0.0065 µM)	3.7 23 13	Metabolism-dependent inhibition	PH-40973	Recombinant CYP 1A1

Source: Clinical Pharmacology Reviewer's table
Positive controls: known inhibitors of respective CYP isoforms
[a] only concentrations up to 50 µM were tested

KINM-180171-ELB, Report PH-40971

At up to the highest test concentration (IC_{50}>50 µM), no change in the inhibitory potency was observed for: finerenone for CYP1A2, 2B6, and 2D6; metabolite M-1a for CYP1A2, 2B6, 2C9, 2C19, and 2D6; metabolite M-1b for CYP1A2, 2B6, 2C19; and metabolites M-2a and M-3a on all investigated CYP isoforms. These findings indicate no metabolism-dependent (time-dependent) inhibition (Table 92). Finerenone inhibited CYPs 2C8, 2C9, and 2C19 after preincubation without NADPH, with IC_{50} values of 6.5, 46, and 19 µM, respectively. Finerenone inhibited CYPS 2C8, 2C9, and 2C19 after preincubation with NADPH, with IC_{50} values of 6.8, 29, and 31 µM, respectively. No relevant change in the inhibitory potency after pre-incubation with NADPH was observed for CYP2C9 and for CYP2C19. A slight increase in the inhibitory potency on CYP2C8 after preincubation with NADPH was observed indicating time-dependent inhibition. However, a concentration-, time-, or NADPH-dependent inhibition of CYP2C8 was not observed (Table 93), indicating no mechanism-based inhibition of CYP2C8 by finerenone. Metabolite M-1a showed inhibitory potency after preincubation with and without NADPH on CYP2C8 and CYP2C9. No or no relevant change in the inhibitory potency after pre-incubation with NADPH was observed for CYP2C8 and for CYP2C9. Metabolite M-1b showed inhibitory potency after preincubation with and without NADPH on CYP2C8. No relevant change in the inhibitory potency after preincubation with NADPH for M-1b on CYP2C8 was observed. There was no relevant change in the inhibitory potency of metabolites M-1a, M-1b, M-2a and M-3a on biotransformation reactions catalyzed by CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 after preincubation with NADPH indicating no metabolism-dependent (time-dependent) inhibition of these metabolites on these CYP isoforms (Table 92).

Table 92. Inhibitory Effects of Finerenone and Metabolites on Formation of Metabolites From Standard Probes After = Pre-Incubation +/- NADPH Mediated by CYP P450 Isoforms = (Duplicate Incubations, Mean Value)

CYP isoform	Probe reaction	IC_{50} for finerenone [µM]	IC_{50} for M-1a [µM]	IC_{50} for M-1b [µM]	IC_{50} for M-2a [µM]	IC_{50} for M-3a [µM]
CYP1A2	Phenacetin *O*-deethylation					
	- NADPH	>50	>50	>50	>50	>50
	+ NADPH	>50	>50	>50	>50	>50
CYP2B6	Bupropion hydroxylation					
	- NADPH	>50	>50	>50	>50	>50
	+ NADPH	>50	>50	>50	>50	>50
CYP2C8	Amodiaquine *N*-deethylation					
	- NADPH	6.5	35	42	>50	>50
	+ NADPH	2.7	35	32	>50	>50
CYP2C9	Diclofenac 4'-hydroxylation					
	- NADPH	46	16	>50	>50	>50
	+ NADPH	35	13	>50	>50	>50
CYP2C19	Mephenytoin 4'-hydroxylation					
	- NADPH	19	>50	>50	>50	>50
	+ NADPH	21	>50	>50	>50	>50
CYP2D6	Dextromethorphan *O*-demethylation					
	- NADPH	>50	>50	>50	>50	>50
	+ NADPH	>50	>50	>50	>50	>50

Source: Study KINM-180171-ELB, Report PH-40971, Table 6-1.
Pre-incubation was 30 min. Concentrations were tested up to 50 µM. Tests were completed in pooled human liver microsomes.

Table 93. Percent Remaining Activity in Formation of Desethylamodiaquine Time-, Concentration-, and NADPH-Dependently With and Without the Presence of Finerenone (Gemfibrozil-O-Glucuronide, Positive Control)

Time [min]	Control (acetonitrile)	Gemfibrozil-*O*-glucuronide 50 µM	Finerenone 2 µM	5 µM	10 µM	20 µM	20 µM (-NADPH)
			[%]				
0	100	100	100	100	100	100	100
10	89	44	104	97	82	88	92
20	93	21	99	98	85	84	96
30	89	15	93	87	84	81	92
40	82	12	90	84	71	71	89
50	78	9	89	79	67	71	89

Source: Study KINM-180171-ELB, Report PH-40971, Table 6-33.

Study KINM-090029-ELB, Report A50906

In Study KINM-090029-ELB (Report A50906), finerenone was tested for potential inhibition against UDP-glucuronosyltransferases (UGTs) in vitro in human liver microsomes. Several UGTs were tested, including UGT1A1, 1A4, 1A6, 1A9, 2B4, and 2B7. The formation of glucuronides of substrates for these UGTs was not inhibited by finerenone, as IC_{50} values were >50 µM.

Study KINM-160003-ELB, Report PH-40043

In Study KINM-160003-ELB (Report PH-40043), the inhibitory potential of metabolites M-1a, M-1b, M-2a, and M-3a against UGTs was assessed. UGTs UGT1A1, 1A4, 1A6, 1A9, 2B4, and 2B7 in the presence and absence of metabolites was investigated. The formation of glucuronides of substrates for these UGTs was not inhibited by the investigated metabolites, as IC_{50} values were >50 μM.

KINM-090191-ELB, Report PH-39130

In Study KINM-090191-ELB (Report PH-39130), finerenone and its major metabolites M-1a, M-1b, M-2a, and M-3a were assessed for the potential to induce CYPs 3A4, 2B6, 2C9, and 1A2. In hepatocyte cultures for three donors, finerenone did not induce CYP1A2 mRNA or activity to the highest concentration tested (90000 μg/L), as the maximum fold-induction was 2.3-fold for mRNA expression and 1.2-fold for CYP activity. Finerenone caused concentration-dependent induction of CYP3A4 mRNA in all three donors, with a maximum induction of 12.5-fold (77% of positive control rifampicin response), 18.2-fold (135% of rifampicin response), and 25.0-fold (110% of rifampicin response), in donors 1 to 3, respectively, in line with the activation of the pregnane X receptor by finerenone. CYP3A4 induction was not observed on CYP3A4 activity levels where a concentration-dependent inhibition was observed for three donors (7 to 10% of vehicle control response, respectively). Induction of CYP2B6 mRNA and CYP2C19 mRNA was observed for finerenone, with maximum increases in CYP2B6 mRNA of 7.9-fold, 6.7-fold, and 6.5-fold, and maximum increases in CYP2C19 mRNA of 3-fold, 2.6-fold, and 1.7-fold.This is in line with the cross-regulation of CYP2B6 and CYP3A4 induction by human pregnane xenobiotic receptor and human constitutive androstane receptor activation. Treatment with finerenone did not cause significant increases in CYP2B6 or CYP2C19 activity, with maximum increases of 1.8-fold, 1.3-fold, and 1.3-fold for CYP2B6, and 1.6-fold, 1.5-fold, and 2.2-fold for CYP2C19 for the three donors tested.

Metabolites M-1a, M-1b and M-2a showed no induction of CYP1A2 in vitro but were identified as inducers of CYP3A4 in cultured hepatocytes, confirmed by PXR activation and induction of co-regulated CYP2B6 and CYP2C19. Consistent with the mRNA results, concentration-dependent increases in CYP3A4 activity over vehicle control were observed for metabolites M-1a, M-1b and M-2a. Metabolite M-3a showed no induction of CYP1A2, CYP3A4, CYP2B6, and CYP2C19 in cultured hepatocytes.

Finerenone and its metabolites were also evaluated as potential inducers of CYP3A4 based on the Relative Induction Score (RIS) correlation method in human hepatocytes from three individual donors. CYP3A4 mRNA results were gathered in response to clinical CYP3A4 inducers pioglitazone (7.9 to 12.2-fold induction), and bosentan (6.7 to 12.6-fold induction) in the three RIS-qualified donors. The results for the positive control inducers and non-inducer penicillin (1.3 to 1.6-fold change of CYP3A4 mRNA levels) demonstrated that the three RIS-qualified donors are suitable to assess CYP3A4 and 1A2 induction potential.

The RIS correlation method was used to assess the drug-drug interaction potential based on in vitro data and clinical exposure data of finerenone and its metabolites. For the assessment of the CYP induction potential, exposure data after multiple oral administrations of 20 mg once daily over 10 days was used. Based on this model, finerenone is predicted to be a weak to moderate inducer with a calculated AUC decrease of midazolam ranging from 43 to 55%, M-1a is predicted to be a weak inducer with a calculated AUC decrease of midazolam ranging from 39 to

40%, and M-2a is predicted to be a weak to moderate inducer with a calculated AUC decrease of midazolam ranging from 45 to 54%.

KINM-110111-ELB, Report PH-39577

Study KINM-110111-ELB (Report PH-39577) was a drug metabolism and PK study that looked at finerenone biotransformation in man. In a clinical Phase 1 study, biotransformation and deposition of finerenone in man was determined by HPLC-LSC analysis of plasma, urine, and feces following a single oral administration of about 10 mg finerenone containing about 2.89 MBq [^{14}C]finerenone. Metabolites observed included naphthyridine metabolite M-1, hydroxylated naphthyridine metabolite M-2, and naphthyridine carboxylic acid metabolite M-3, dihydrodiol metabolites M-4, M-5 and M-8, hydroxylated dihydronaphthyridine M-7, dihydronaphthyridine carboxylic acid M-9, and metabolite M-10 (resulting from several phase I biotransformation reactions). Total radioactivity excreted into urine and feces was 100.9±8.70% (range 88.0 to 106.3%) indicating complete recovery. The amount of radioactivity excreted into urine was $\%A_{E,ur}(0\text{-}t_{last})$ =79.6±3.04% (range 76.2 to 83.3%), whereas the amount of the radioactivity excreted into feces was $\%A_{E,fec}(0\text{-}t_{last})$ =21.2±7.93% (range 9.63 to 26.9%).

Total radioactivity plasma AUC showed finerenone covered 7.1%, metabolite M-1 covered 48.9%, metabolite M-2 covered 21.5%, metabolite M-3 covered M-3 9.0%, metabolite M-4 covered 2.4%, and metabolite M-5 covered 1.4%. Based on these percentages, metabolites M-1a (38.8%), M-1b (10.1%) and M-2a (20.3%) were identified as major human plasma metabolites (accounting for >10% of total radioactivity plasma AUC). Exposure data from patients with impaired renal function (Study 14509) identified M-3a as major human plasma metabolite as well (~30% of total drug related plasma AUC in renally impaired patients). Based on data from this study, renal impairment study, and the atropisomer ratio after multiple dose administration (Study 13785), metabolites M-1a, M-1b, M-2a and M-3a are regarded as major human plasma metabolites. Unchanged finerenone represented about 0.184% of the administered dose in feces and 0.825% in urine. Metabolites M-2, M-3, and M-4 were preferentially excreted via urine, whereas M-5 is predominantly excreted via feces. Naphthyridine carboxylic acid metabolite M-3 was the main component excreted, accounting for 47.8% of the dose (46.3% via urine and 1.48% via feces). Atropisomer ratios in plasma, urine, and feces are shown for finerenone in Table 94.

Table 94. Atopisomer Ratio (Arithmetic Mean, n=4) in Plasma, Urine, and Feces of Healthy Male Subjects Following Single Oral Administration of 9.27 to 9.36 mg Finerenone Containing 2.87 to 2.90 MBq [^{14}C]Finerenone From Study 14502

Matrix	Plasma[a] AUC(0-48)	Urine[b] 0-48 h	Feces[a] 0-96 h	Urine + feces[c]
M-1a	79.3 (mean)	n.a.	86.0 (mean)	86.0 (mean)
	80.4 (b) (6)		88.4 (b) (6)	
	78.1		84.6	
	80.3		85.5	
	78.4		87.3	
M-1b	20.7 (mean)	n.a.	14.0 (mean)	14.0 (mean)
	19.6 (b) (6)		11.6 (b) (6)	
	21.9		15.4	
	19.7		14.5	
	21.6		12.7	
M-2a	94.6 (mean)	93.9 (mean)	91.6 (mean)	93.6 (mean)
	94.7 (b) (6)	93.1 (b) (6)	93.4 (b) (6)	
	92.4	92.9	87.9	
	95.6	94.9	92.8	
	95.2	93.7	91.8	
M-2b	5.4 (mean)	6.1 (mean)	8.4 (mean)	6.4 (mean)
	5.3 (b) (6)	6.9 (b) (6)	6.6 (b) (6)	
	7.6	7.1	12.1	
	4.4	5.1	7.2	
	4.8	6.3	8.2	
M-3a	99.1 (mean)	97.8 (mean)	78.7 (mean)	97.3 (mean)
	98.8 (b) (6)	97.7 (b) (6)	85.9 (b) (6)	
	98.2	98.2	76.6	
	99.5	97.7	77.0	
	99.4	97.8	77.6	
M-3b	0.9 (mean)	2.2 (mean)	21.3 (mean)	2.7 (mean)
	1.2 (b) (6)	2.3 (b) (6)	14.1 (b) (6)	
	1.8	1.8	23.4	
	0.5	2.3	23.0	
	0.6	2.2	22.4	

a = LC-MSMS, plasma: geometric mean, feces: arithmetic mean based on total excretion
b = LC-HRMS, arithmetic mean based on total excretion
c = calculation based on excretion *via* urine and feces

Source: Applicant, Study KINM 110111-ELB, Report PH-39577, Table 5-2.
Abbreviations: AUC, area under the curve

14.1.3. Transporter Characterization

Study KINE 170226-EXT, Report R-12248

This study was a permeability assessment of finerenone using Caco-2 cell monolayers. Finerenone is a high permeability compound in Caco-2 cells based on the efflux ratios (Table 95).

Table 95. Bidirectional Caco-2 Permeability and Recovery of Finerenone

Treatment BAY 94-8862 (µM)	Replicate	AP-to-BL P_{app} (10^{-6} cm/s)	AP-to-BL Recovery (%)	BL-to-AP P_{app} (10^{-6} cm/s)	BL-to-AP Recovery (%)	Efflux Ratio
2	1	16.5	90.4	44.9	98.4	2.30
	2	20.5	109	40.6	106	
	3	20.4	111	46.4	102	
	Average	19.1	103	43.9	102	
	SD	2.2	11	3.0	4	
21	1	21.6[a]	94.7	40.0	85.7	1.50
	2	22.3	97.8	34.2	95.1	
	3	26.6	97.0	36.1	97.2	
	Average	24.5	96.5	36.8	92.6	
	SD	N.D.	1.6	2.9	6.1	
210	1	35.0	105	29.8	86.0	0.857
	2	29.9	106	21.9	89.3	
	3	31.8	111	31.1	88.8	
	Average	32.2	107	27.6	88.1	
	SD	2.6	4	5.0	1.8	

[a] The P_{app} of lucifer yellow was greater than 0.8×10^{-6} cm/s in the PE, suggesting the compromise of the cell monolayer. It was excluded from the calculation of the average.
Source: Applicant, Study KINE 170226-EXT, Report R-12248, Table 10.
Abbreviations: AP, apical; BL, basolateral; ND, not determined

Studies KINE 180150-ELB and KINE 180151-ELB, Report PH-40755

This study showed that finerenone was a substrate for human P-gp. Efflux ratios were calculated for L-MDR1 cells and in wild-type LLC-PK1 cells. The ratio of ratios (L-MDR1/LLC-PK1) was calculated. Data are presented in Table 96.

Table 96. Transport of Finerenone Across L-MDR1 and LLC-PK1 Cells

BAY 94-8862 concentration	L-MDR1 Efflux ratio		LLC-PK1 Efflux ratio		L-MDR1/LLC-PK1 Ratio of ratios	
[µM]	Mean [nm/s]	SD [nm/s]	Mean [nm/s]	SD [nm/s]	Mean	SD
2.0	6.9	1.40	0.78	0.09	8.9	0.03
20	5.8	0.93	0.64	0.05	8.9	0.02
100	4.2	1.63	0.64	0.07	6.6	0.06

Source: Applicant, Study KINE 180150-ELB and KINE 180151-ELB, Report PH-40755, Table 3.

Study KINE 130073-ELB, Report PH-40886

This study investigated the inhibitory potential of finerenone, M-1a, M-1b, M-2a, and M-3a towards P-gp. Data are presented in Table 97. A bi-directional transport assay using P-gp-transfected LLC-PK1 cells (L-MDR1 cells) and LLC-PK1 wild-type cells (control cells) was performed to determine the inhibitory potential. For M-2a and M-3a, IC50 values were not reached.

Table 97. Inhibitory Potential of Finerenone and Metabolites on P-gp

Test Article	Probe Substrate	IC_{50} (µM)	Conclusion
Finerenone	Dipyridamole (2µM)	47	P-gp inhibitor
	Digoxin (20µM)	121	

Test Article	Probe Substrate	IC_{50} (µM)	Conclusion
M-1a	Dipyridamole (2µM)	70	Some inhibitory potential
	Digoxin (20µM)	ND	
M-1b	Dipyridamole (2µM)	30.9	Some inhibitory potential
	Digoxin (20µM)	ND	

Source: Clinical Pharmacology Reviewer's table\
Abbreviations: ND, not determined

Study KINE 120126-ELB, Report PH-40764

This study showed that finerenone is not a substrate for human BCRP. Efflux ratios across MDCKII-BCRP cells were measured. The ratio was also measured in wild type cells, then the ratio of ratios was calculated (MDCKII-BCRP/MDCKII-WT). Results are presented in Table 98.

Table 98. Transport of Finerenone Across MDCKII-BCRP and MDCKII-WT Cells

	MDCKII-BCRP		MDCKII-WT		MDCKII-BCRP / MDCKII-WT	
BAY 94-8862 concentration	Efflux ratio		Efflux ratio		Ratio of ratios	
[µM]	Mean [nm/s]	SD [nm/s]	Mean [nm/s]	SD [nm/s]	Mean	SD
0.2	1.3	0.13	1.1	0.05	1.2	0.09
2	1.1	0.04	0.99	0.1	1.1	0.10
20	0.86	0.08	0.8	0.07	1.1	0.27
100	0.5	0.05	0.55	0.06	0.9	0.16

Source: Applicant, Study KINE 120126-ELB, Report PH-40764, Table 3.

Study KINE 140015-ELB, Report PH-40885

The inhibitory potential of finerenone and M-1a, M-1b, M-2a, and M-2a toward BCRP was evaluated. Data are presented in Table 99. A bi-directional transport assay using BCRP-transfected MDCKII cells (MDCKII-BCRP cells) and MDCKII wild-type cells (control cells) was performed to determine the inhibitory potential. IC_{50} values were not reached for M-1a, M-1b, M-2a, and M-3a.

Table 99. Inhibitory Potential of Finerenone and Metabolites on BCRP

Test Article	Probe Substrate	IC_{50} (µM)	Conclusion
Finerenone	Topotecan (2µM)	18.1±3	BCRP inhibitor
	PhiP[a] (2µM)	17.4±3	

Source: Clinical Pharmacology Reviewer's table
[a] PhiP: 2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
Abbreviations: BCRP, breast cancer resistant protein

Study KINE 140174-EXT, Report R-9574

This study looked at the human uptake transporters OATP1B1 (SLCO1B1) and OATP1B3 (SLCO1B3). The hepatic uptake transporters hOATP1B1 and hOATP1B3 are localized at the basolateral (sinusoidal) plasma membrane domain of hepatocytes. HEK293 cell lines expressing hOATP1B1 and hOATP1B3 were used to determine the substrate characteristics of finerenone towards hOATP1B1 and hOAT1B3.

The uptake of 0.5 µM and 5 µM ^{14}C-finerenone was determined in the absence and presence of the probe substrate, estrone 3-sulfate (ES) (10 µM), in hOATP1B1-transfected and vector-transfected HEK cells. The probe inhibitor used in the assay was rifampicin at 50 µM.

hOATP1B1-expressing HEK cells showed no higher ^{14}C-finerenone uptake velocity compared to vector-transfected HEK cells. The probe substrate ES (10 µM), as well as the probe inhibitor rifampicin (50 µM), showed no effect on the uptake of [14C]finerenone, indicating that finerenone is not a substrate of hOATP1B1 in vitro.

The uptake of 0.5 µM and 5 µM [14C]finerenone was determined in the absence and presence of the probe substrate, sulfobromophthalein (10 µM), in hOATP1B3-transfected and vector-transfected HEK cells. The probe inhibitor used in the assay was rifampicin at 5 µM. hOATP1B3-expressing HEK cells showed no higher [14C]finerenone uptake velocity compared to vector-transfected HEK cells. The probe substrate sulfobromophthalein (10 µM), as well as the probe inhibitor rifampicin (5 µM), showed no effect on the uptake of [14C]finerenone, indicating that finerenone is not a substrate of hOATP1B3 in vitro.

Study KINE 190017-ELB, KINE 190018-ELB, KINE 190019-ELB, KINE 190020-ELB, KINE 190021-ELB, Report PH-40952

This study evaluated the inhibitory potential of finerenone and M-1a, M-1b, M-2a, and M-3a on OATP1B1 and OATP1B3 after preincubation. The influence of these test articles was determined on the uptake of pravastatin, an OATP probe substrate. Rifamycin was used as a positive control. Concentrations were evaluated up to 10 µM. For the OATP1B1 transporter, finerenone, M-1a, and M-1b IC_{50} values were 3.2, 3.8, and 3.9 µM, respectively. For the OATP1B3 transporter, M-1a, M-1b, and M-3a IC_{50} values were 7.6, 7.3, and 3.4 µM, respectively.

Study KINE 140041-EXT, Report R-9494

This study assessed inhibition of finerenone toward OAT1 and OAT3 in transporter transfected HEK cells. At 0.3 and 3µM, finerenone did not show any inhibition towards OAT1 or OAT3. For OAT1, the percentage inhibition was -18.9±5 and -4.56±5.71 for 0.3 and 3µM, respectively. For OAT3, the percentage inhibition was -237. ±7.5 and -12.6±2.9 for 0.3 and 3µM, respectively.

Study KINE 140103-EXT, Report R-9702

Assessment of M-1a, M-1b, M-2a, and M-3a as inhibitors of OAT1 and OAT3 was performed in transporter-transfected HEK cells. Inhibition percentages are presented in Table 100. M-1b, M-2a, and M-3 appeared to show some inhibitory potential towards OAT3.

Table 100. Inhibitory Potential of M-1a, M-1b, M-2a, and M-3a on OAT1 and OAT3

Test article	Treatments (μM)	Known inhibitor (μM)	Percentage inhibition towards OAT1	Percentage inhibition towards OAT3
BAY 1117267 (M-1a)	0.247		-11.2 ± 4.6	3.40 ± 7.56
	2.47		-20.4 ± 4.9	7.63 ± 3.76
BAY 1117266 (M-1b)	0.516		-9.79 ± 3.93	9.69 ± 5.42
	5.16		0.418 ± 3.97	24.3 ± 4.3
BAY 1117268 (M-2a)	0.310		-13.8 ± 7.0	22.2 ± 8.9
	3.10		-23.0 ± 5.7	21.4 ± 4.2
BAY 1117271 (M-3a)	0.425		-10.2 ± 3.8	26.4 ± 7.7
	4.25		-14.4 ± 6.0	20.9 ± 5.3
		Probenecid (100)	96.4 ± 0.5	100

Source: Applicant, Study KINE 140103-EXT, Report R-9702, Table on Page 7 of Report R-9702.

Study KINE 160025, Report R-11129

This study evaluated finerenone inhibition potential of taurocholate biliary clearance in Sandwich-Cultured Transporter Certified™ Human Hepatocytes using B-CLEAR® Technology. No significant inhibition (>50% of control) of TCA biliary clearance observed. The biliary excretion index (BEI) of d8-TCA was also not significantly inhibited in sandwich-cultured human hepatocytes exposed to increasing concentrations of finerenone.

Study KINE 150089-EXT, Report R-11130

This study evaluated M-1a, M-1b, M-2a, and M-3a inhibition potential of taurocholate biliary clearance in Sandwich-Cultured Transporter Certified™ Human Hepatocytes using B-CLEAR® Technology. No significant inhibition (>50% of control) of TCA biliary clearance was observed for M-1a, M-1b, M-2, or M-3a at any concentration (0.03 to 30μM). Consistent with TCA biliary clearance results, the BEI of d8-TCA was also not significantly (>50% of control) inhibited. The BEI of d8-TCA ranged from 105% to 93.0%, 105% to 94.2%, 101% to 96.6%, and 100% to 95.9% of control in SCHH treated with increasing concentrations of M-1a, M-1b, M-2a, and M-3a, respectively, for concentrations between 0.03 to 30μM.

Study KINE 140264-EXT, Report R-11196

This study determined the inhibitory potential of finerenone to renal efflux transporters MATE1 and MATE2K performed with transporter-transfected HEK cells. Metformin was the probe substrate. At 5 μM, BAY 94-8862 showed 10.1±5.8% inhibition towards MATE1 and 35.2±14.9% inhibition towards MATE2K.

Study KINE 160086-EXT, Report R-11820

This study determined the inhibitory potential of M-1a (BAY 1117267), M-1b (BAY 1117266), M-2a (BAY 1117268) and M-3a (BAY 1117271) on renal efflux transporters MATE1 and MATE2K. The tested concentrations for each test article were 0.5 and 5µM. At the concentrations tested, no test article showed >50% inhibition. Cimetidine and pyrimethamine were used as positive controls for MATE1 and MATE2K, respectively.

Study KINE 140042-EXT, Study R-9495

This study assessed the substrate and inhibitor potential of finerenone on OCT1 on transporter transfected HEK cells. The influx rate ratios against a vector control indicate that finerenone is not a substrate of OCT1 at 0.1 and 0.5µM with incubations up to 10 minutes. Influx rate ratios were less than 2 under all conditions (ranging from 1.00 to 1.1 at 0.1µM and 1.04 to 1.11 at 0.5µM). Inhibitory assessment of finerenone towards OCT1 was performed in transporter transfected HEK cells. At 0.5 and 5µM, finerenone did not show any inhibition towards OCT1.

Study KINE 140043-EXT, Report R-9440

This study assessed the inhibitory potential of finerenone toward OCT2 with transfected HEK cells. The percentage inhibition of 0.3 and 3µM of finerenone towards OCT2 was less than 4%, with percentage inhibition towards OCT2 at 3.66±5.39% and 1.14±8.34% at 0.3 and 3µM, respectively.

Study KINE 140104-EXT, Report R-9701

This study assessed the inhibitory potential of M-1a, M-1b, M-2a, and M-3a on hepatic and renal uptake transporters OCT1 and OCT2. No inhibition was seen towards OCT1. Inhibition of OCT2 was mostly minimal, though M-1b had 17.4±8.5% inhibition towards OCT2.

Study KINM 190005-ELB, Report PH-41050

In this study, potential drug interactions of finerenone with SGLT2 inhibitors were studied, as SGLT2 inhibitors are expected to be a common comedication. The inhibitory effect of finerenone on the metabolic clearance of canagliflozin, dapagliflozin, empagliflozin, ipragliflozin, and tofogliflozin was investigated in vitro in cryopreserved human hepatocytes. A potential change in AUC (AUCR) was calculated for the SGLT2 inhibitors based on in vitro clearance with/without finerenone. At a concentration at least 5-fold above clinically relevant finerenone concentrations (<1 µM), the clearance of none of the tested SGLT inhibitors was significantly inhibited. Empagliflozin could not be assessed due to low turnover in hepatocytes.

14.2. In Vivo Studies

Single Dose, Basic Phase I Dose Escalation Study in a Randomized, Single-Blind, Placebo-Controlled, Group-Comparison Design to Investigate Safety and Tolerability of BAY 94-8862 and Its Pharmacodynamics and Pharmacokinetics After Oral Dosing in 8 Healthy Male Subjects per Dose Step (Study 13782)

Study Design

The primary objective of the study was to investigate the safety and tolerability of finerenone after a single oral dose starting at 1 mg up to 40 mg administered as a polyethylene glycol (PEG)-based solution in healthy male subjects. The secondary objectives were to investigate the PD and PK of finerenone. Participants were healthy white males aged 18 to 45 years with a BMI between 18 and 29.9 kg/m^2. Pharmacodynamic assessments included blood pressure, heart rate, heart rate over 1 minute, and standing blood pressure; neurohormones including plasma renin activity, serum angiotensin II, serum aldosterone, and serum noradrenalin; and changes in urine including urinary volume, sodium, potassium, magnesium, calcium, ratio of urinary sodium/potassium, the log10 of urinary sodium/potassium ratio, and the log10 of 10*urinary sodium/potassium ratio. PK parameters included AUC and C_{max} as primary parameters. Secondary PK parameters included AUC/D, AUC_{norm}, C_{max}/D, $C_{max,norm}$, t_{max}, $t_{1/2}$, mean residence time, CL/f, VZ/f, $AUC_{(0-tn)}$, and $AUC_{(0-tn)norm}$ for all doses, and $Ae_{ur,}$ and CL_R only in the 40-mg dose group. All treatments were administered in the fasted state.

Results

Table 101. PK Parameters of Finerenone (Geometric Mean/%CV [Range]) After Administration of Finerenone in a PEG-Based Solution (BAY 94-8862 1 mg, 2.5 mg, and 5 mg)

Parameter	Unit	BAY 94-8862 1 mg n=5	BAY 94-8862 2.5 mg n=5	BAY 94-8862 5 mg n=6
AUC	µg*h/L	12.99/29.7 (9.819-21.20)	25.23/17.1 (20.96-31.90)	51.13/51.4 (29.10-102.7)
AUC_{norm}	kg*h/L	1.015/35.3 (0.6866-1.753)	0.7723/14.6 (0.6197-0.9133)	0.8181/54.8 (0.4196-1.567)
AUC/D	$h/L*10^{-3}$	12.97/29.6 (9.809-21.12)	10.07/17.0 (8.374-12.71)	10.04/51.4 (5.703-20.09)
C_{max}	µg/L	5.431/27.3 (4.427-8.462)	12.54/11.6 (10.96-13.95)	25.45/38.0 (14.52-42.86)
$C_{max,norm}$	kg/L	0.4243/31.7 (0.3096-0.6996)	0.3837/10.3 (0.3539-0.4516)	0.4072/38.5 (0.2504-0.6540)
C_{max}/D	$1/L*10^{-3}$	5.423/27.2 (4.423-8.428)	5.001/11.7 (4.372-5.575)	4.996/38.0 (2.845-8.384)
t_{max}[a]	h	0.5000 (0.5000-0.5000)	0.5000 (0.2500-0.5000)	0.5000 (0.2500-0.5000)
$t_{1/2}$	h	1.702/11.7 (1.429-1.909)	1.741/19.0 (1.379-2.212)	1.874/14.2 (1.507-2.177)
MRT	h	2.684/8.0 (2.372-2.945)	2.547/11.7 (2.237-2.813)	2.664/12.0 (2.208-3.049)
V_z/f	L	189.4/24.8 (130.4-251.9)	249.6/8.8 (235.5-290.1)	269.3/42.2 (140.7-457.1)
CL/f	L/h	77.12/29.6 (47.35-101.9)	99.35/17.0 (78.67-119.4)	99.63/51.4 (49.79-175.4)

Source: Applicant, Study 13782 Report, Table 2-1
[a] Median (range)
[b] Arithmetic mean/SD (range)
Abbreviations: AUC, area under the curve; CL, clearance; CV, coefficient of variation; MRT, mean residence time; PEG, polyethylene glycol; PK, pharmacokinetic

Table 102. PK Parameters of Finerenone (Geometric Mean/%CV [Range]) After Administration of Finerenone in a PEG-Based Solution (BAY 94-8862 10 mg, 20 mg, and 40 mg)

Parameter	Unit	BAY 94-8862 10 mg n=6	BAY 94-8862 20 mg n=6	BAY 94-8862 40 mg n=6
AUC	µg*h/L	132.1/59.1 (82.60-362.6)	161.4/30.1 (108.2-233.5)	470.3/45.3 (229.0-757.3)
AUC_{norm}	kg*h/L	1.071/62.7 (0.6082-3.073)	0.6555/25.1 (0.4817-0.9233)	0.8901/43.6 (0.4409-1.389)
AUC/D	$h/L*10^{-3}$	13.18/59.1 (8.241-36.15)	8.045/30.1 (5.397-11.67)	11.75/45.3 (5.725-18.93)
C_{max}	µg/L	42.49/55.7 (21.16-90.73)	63.58/25.6 (47.92-96.44)	154.4/44.1 (92.32-317.6)
$C_{max,norm}$	kg/L	0.3444/51.8 (0.1900-0.7690)	0.2583/29.2 (0.1856-0.4140)	0.2922/48.3 (0.1777-0.6903)
C_{max}/D	$1/L*10^{-3}$	4.240/55.8 (2.111-9.047)	3.170/25.7 (2.391-4.814)	3.857/44.1 (2.308-7.935)
t_{max}[a]	h	0.6250 (0.2500-2.000)	0.7500 (0.5000-1.500)	1.000 (0.7500-3.000)
$t_{1/2}$	h	2.066/23.3 (1.683-3.228)	1.776/11.2 (1.439-1.927)	2.834/41.3 (1.635-4.124)
MRT	h	3.054/18.7 (2.299-3.944)	2.793/12.6 (2.402-3.294)	3.161/16.9 (2.548-4.023)
V_z/f	L	226.1/35.1 (128.8-343.1)	318.5/27.6 (232.5-503.1)	348.0/25.8 (243.9-479.8)
CL/f	L/h	75.86/59.1 (27.66-121.3)	124.3/30.1 (85.71-185.3)	85.10/45.3 (52.82-174.7)
Ae_{ur}[b]	µg	-	-	227.9/56.85 (160.3-327.0)
$\%Ae_{ur}$[b]	%	-	-	0.5695/0.1420 (0.4007-0.8171)
CL_R	L/h	-	-	0.4728/38.5 (0.2514-0.6999)

Source: Applicant, Study 13782 Report, Table 2-1
[a] Median (range)
[b] Arithmetic mean/SD (range)
Abbreviations: AUC, area under the curve; CL, clearance; CV, coefficient of variation; MRT, mean residence time; PEG, polyethylene glycol; PK, pharmacokinetic

Table 103. Summary of ANOVA on Logarithm of Parameters of Finerenone in Plasma for Dose Proportionality

Parameter	Degrees of freedom	Mean sum of squares	F value	*P* value
AUC_{norm}	5	0.1893	1.13	0.3690
$C_{max,norm}$	5	0.2206	1.64	0.1818
AUC/D	5	0.2051	1.28	0.3009
C_{max}/D	5	0.2291	1.80	0.1463

Source: Applicant, Study 13782 Report, Table 9-4.
Abbreviations: ANOVA, analysis of variance; AUC, area under the curve

Reviewer's Comment

The pharmacodynamic endpoints were not significantly affected by finerenone. Finerenone did not have an effect on blood pressure, heart rate, or neurohormones after a single dose in healthy subjects. Electrolyte changes in the urine were not consistent or clinically relevant.

In general, finerenone was rapidly absorbed, reaching t_{max} within an hour. Half-life ranged from 1.7 to 2.8 hours. Only a small amount (about 0.57% of dose) was eliminated renally as unchanged finerenone by glomerular filtration (Table 101 and Table 102). When evaluating for dose-proportionality, finerenone AUC increased dose-proportionally; however, C_{max} increase with increasing dose was slightly less than proportional (Table 103).

Multiple Dose Basic Phase I Dose Escalation Study, to investigate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of BAY 94-8862 After Oral Dosing of 10 mg BID, 20 mg BID or 40 mg OD Over 10 Days Given as 10 mg IR-tablets in 12 Healthy Male Subjects per Dose Step in a Randomized, Single-Blind, Placebo-Controlled, Group-Comparison Design (Study 13785)

Study Design

The primary objective of this study was to investigate the safety and tolerability of finerenone after multiple oral doses of 10 mg BID, 20 mg BID, and 40 mg once daily given as 10 mg IR tablets over 10 days in 12 healthy male subjects (9 finerenone and 3 placebo) per dose step (Part A of the study). The secondary objectives were to assess the PD of finerenone and PK of finerenone and the three main metabolites (Part A of the study), and to assess the influence of multiple oral doses of finerenone given as 20 mg BID over 10 days on the PK of a single oral 7.5-mg doses of midazolam, a CYP3A4 substrate, administered on Days -1, 2, and 10, in 9 healthy male subjects (Part B of the study). Participants were healthy white male subjects aged 18 to 45 years, with a BMI of 18 to 29.9 kg/m^2.

PD parameters in Part A of the study were heart rate over 1 minute, heart rate and blood pressure, neurohormones (plasma renin-activity, plasma angiotensin II, serum aldosterone and plasma noradrenaline), urinary electrolytes (sodium, potassium, magnesium), urinary creatinine, and urinary volume.

Results

There did not appear to be a consistent relevant increase in natriuresis or reduction in urine potassium after multiple oral doses of 10 mg BID, 20 mg BID, or 40 mg once daily finerenone administered as IR tablets.

Table 104. PK Parameters of Finerenone in Plasma Following a Single (First) Dose of 10 mg, 20 mg, or 40 mg Finerenone on Day 1 (Geometric Mean/%CV [Range])

Parameter	Unit	N	10 mg bid BAY 94-8862	N	20 mg bid BAY 94-8862	N	40 mg od BAY 94-8862
AUC	µg*h/L	11	208.3/34.7 (144.5-399.9)	9	318.5/21.3 (252.8-491.2)	9	928.7/62.2 (505.8-2612)
AUC_{norm}	kg*h/L	11	1.571/32.8 (1.023-3.079)	9	1.300/25.4 (0.8597-1.989)	9	1.822/53.3 (1.049-4.396)
AUC/D	$h/L*10^{-3}$	11	20.83/34.7 (14.45-39.99)	9	15.93/21.3 (12.64-24.56)	9	23.22/62.2 (12.64-65.31)
C_{max}	µg/L	11	90.54/37.3 (54.05-165.4)	9	177.3/40.0 (82.91-271.0)	9	287.2/44.8 (169.2-570.2)
$C_{max,norm}$	kg/L	11	0.6830/30.7 (0.4756-1.149)	9	0.7233/44.3 (0.3151-1.097)	9	0.5633/36.7 (0.3511-0.8838)
C_{max}/D	$1/L*10^{-3}$	11	9.054/37.3 (5.405-16.54)	9	8.863/40.0 (4.145-13.55)	9	7.179/44.8 (4.230-14.25)
$t_{½}$	h	11	1.779/13.7 (1.435-2.128)	9	1.685/10.9 (1.469-1.947)	9	3.044/27.5 (1.709-4.405)
t_{max}[a]	h	11	0.7500 (0.5000-1.500)	9	0.5000 (0.5000-1.500)	9	0.7500 (0.5000-2.000)

Source: Applicant, Study 13785, Report PH-36896, Table 2-2.
[a] Median (Range)
Abbreviations: AUC, area under the curve; CV, coefficient of variation; PK, pharmacokinetics; C_{max}, maximum drug concentration in plasma; Tmax, time to reach maximum drug concentration in plasma; t1/2, half-life associated with the terminal slope

Table 105. PK Parameters of Finerenone in Plasma Following Multiple Oral Administrations of 10 mg BID, 20 mg BID, or 40 mg OD over 10 Days, or of 20 mg BID Finerenone over 10 Days and Three Single Oral Doses of 7.5 mg Midazolam on Days 1, 2, and 10, Respectively (Geometric Mean/%CV [Range])

Parameter	Unit	N	10 mg bid BAY 94-8862	N	20 mg bid BAY 94-8862	N	40 mg od BAY 94-8862	N	20 mg bid BAY 94-8862 + midazolam
$AUC_{\tau,md}$	µg*h/L	9	232.5/32.7 (151.8-444.1)	9	420.7/27.4 (252.2-587.0)	9	1022/55.4 (491.3-2585)	8	661.0/22.4 (438.6-879.3)
$AUC_{\tau,md,norm}$	kg*h/L	9	1.812/33.9 (1.107-3.420)	9	1.717/28.2 (1.034-2.499)	9	2.005/52.0 (1.019-5.363)	8	2.430/14.8 (1.864-3.030)
$AUC_{\tau,md}/D$	$h/L*10^{-3}$	9	23.25/32.7 (15.18-44.41)	9	21.04/27.4 (12.61-29.35)	9	25.55/55.4 (12.28-64.62)	8	33.05/22.4 (21.93-43.97)
$C_{max,md}$	µg/L	9	94.54/30.9 (56.30-138.5)	9	170.6/39.2 (93.69-269.5)	9	258.6/27.3 (151.4-352.5)	8	167.2/35.4 (116.2-305.7)
$C_{max,md,norm}$	kg/L	9	0.7367/32.4 (0.3828-1.066)	9	0.6960/41.6 (0.3841-1.198)	9	0.5072/25.5 (0.3142-0.7314)	8	0.6147/16.0 (0.4998-0.8558)
$C_{max,md}/D$	$1/L*10^{-3}$	9	9.454/30.9 (5.630-13.85)	9	8.529/39.2 (4.685-13.47)	9	6.464/27.3 (3.785-8.812)	8	8.360/35.4 (5.812-15.28)
$t_{½}$	h	9	2.564/46.7 (1.565-5.695)	9	2.832/39.7 (1.520-4.481)	9	3.112/36.7 (1.866-6.633)	8	4.295/67.3 (2.559-16.04)
R_AC_{max} (R_{A1})	%	9	118.9/25.6 (69.00-152.2)	9	96.23/46.7 (41.09-179.9)	9	90.04/36.5 (53.31-149.2)		
R_AAUC (R_{A3})	%	9	121.2/11.3 (105.9-148.0)	9	133.2/25.2 (95.16-190.3)	9	110.5/35.0 (53.45-193.0)		
R_{Lin}	%	9	119.9/11.6 (105.0-147.2)	9	132.1/25.3 (94.82-189.0)	9	110.0/35.1 (52.93-192.4)		
$t_{max,md}$[a]	h	9	0.7500 (0.5000-2.000)	9	0.7500 (0.5000-2.500)	9	1.000 (0.5000-1.500)	8	0.5000 (0.5000-1.000)

Source: Applicant, Study 13785, Report PH-36896, Table 2-3.
[a] Median (Range)
Abbreviations: AUC, area under the curve; BID, twice daily; CV, coefficient of variation; OD, once daily; PK, pharmacokinetics; C_{max}, maximum drug concentration in plasma; t1/2, half-life associated with the terminal slope; RA, accumulation ratios

Reviewer's Comment

There was not a consistent change in the C_{max} of finerenone when administered over several days; however, there was a modest increase in $AUC_{\tau,md}$ compared to AUC after the first dose. After multiple doses, M-1 was the most prominent analyte in plasma, and M-2 also had increased exposure to the parent drug. Urinary excretion was highest for M-3. Finerenone administration with midazolam resulted in a slight change in the AUC of midazolam and its metabolite, increasing the AUC on day 10 by 21% and 18%, respectively. This is evidence that at 20 mg BID, finerenone acts as a weak CYP3A4 inhibitor.

In Part A, finerenone administration did not affect blood pressure, heart rate, or heat rate over 1 minute after repeated doses of 10 mg BID, 20 mg BID, or 40 mg once daily over 10 days in healthy subjects (Table 104); however, after 10 days of dosing, there was a statistically significant increase in plasma-renin activity in the 10 mg BID and 20 mg BID treatment groups (Table 105). There was also an increase in serum aldosterone in the 20 mg BID and 40 mg once daily treatment groups compared to placebo. These increases reversed within 48 hours. The increases in these parameters indicate that there was activation of the renin-angiotensin-

aldosterone system and that the drug was pharmacologically active. There were no clinically relevant effects on serum electrolytes in healthy subjects.

Single center, Open-Label, Non-Placebo-Controlled, Single-Dose Study in Healthy Male Subjects to Compare the Bioavailability of 10 mg Finerenone Aqueous Oral Solution and Tablet (Part A; Randomized) and to Investigate the Metabolism, Excretion Pattern and Mass Balance of 10 mg [^{14}C]Finerenone Oral Solution (Part B; Non-Randomized) (Study 14502)

Study Design

The primary objective in Part A was to investigate the bioavailability of the aqueous solution of finerenone compared to a 10 mg IR tablet in healthy male subjects in order to decide on the use of this formulation versus the alternative option (PEG solution) in Part B of the study. The primary objectives in Part B of the study were to measure the cumulative amount as well as the time course of the drug-related, radiolabeled material excreted in the urine and feces following a single dose of 10 mg [^{14}C]finerenone (oral solution); to characterize the metabolite pattern in plasma, urine, and feces and to identify metabolites where possible; to quantify total radioactivity in blood and plasma; and to quantify finerenone and metabolites circulating in plasma, if possible. The test drug in Part A was finerenone aqueous solution (2 mg/mL), and the test drug in Part B was [^{14}C]finerenone (specific radioactivity: 0.31 MBq/mg) aqueous solution (2 mg/mL). The dose was 10 mg for each test drug. The participants were healthy male subjects aged 45 to 65 years with a BMI of 18 to 30 kg/m^2. Part A was a single-center, open-label, non-placebo-controlled, randomized, two-fold crossover study, and Part B was a single-center, non-randomized, open-label, non-placebo-controlled study.

Results

Finerenone was rapidly absorbed from both the tablet and the aqueous solution with t_{max} for the solution occurring at 0.5 h and tablet at 0.75 h. The relative bioavailability was 103% for the aqueous solution compared to the IR tablet, which was an improvement over the PEG solution, which previously demonstrated a relative bioavailability of 53% relative to the tablet formulation. Therefore, the aqueous solution was chosen for Part B of the study.

Part B was the mass-balance study of finerenone. The blood to plasma ratio calculated from the geometric mean values indicated that radioactivity is mostly in the plasma and not in the blood cells, with an AUC ratio of 0.65. The AUC of finerenone accounted for about 7% of the AUC of total radioactivity, and the total radioactivity in the plasma was eliminated with an estimated half-life of 17.4 hours. No radioactivity was detected in the blood after 2 days, and no radioactivity was detected in plasma after 3 days.

79.6% of the total finerenone-associated radioactivity was excreted via urine, with 77% excreted by 2 days post-dose. 21.2% of the radioactivity was excreted via feces, with 19.9% excreted by 4 days post-dose. Inter-subject variability was higher for excretion in feces (9.6% to 26.9%) compared to urine (76.2% to 83.3%).

Reviewer's Comment

Whole blood to plasma ratio for AUC for total radioactivity was 0.65, indicating that the total finerenone-associated radioactivity was largely in plasma and not in blood cells. The AUC of

finerenone accounted for about 7% of the total radioactivity in plasma. The parent drug and total radioactivity were eliminated from plasma with estimated half-lives of about 2 h and 17 h, respectively, indicating the presence of metabolites in plasma, with slower elimination compared to finerenone. Nearly 80% of the radioactivity was excreted via urine, and about 21% was excreted via the feces.

Relative Bioavailability Study to Investigate the Pharmacokinetic Dose Proportionality, Safety and Tolerability of Single Oral Doses of Finerenone 10-mg Tablet in Comparison to 20-mg Tablet in the Fasting Condition and to Investigate the Effect of a High Fat, High Calorie Meal on the 20-mg Tablet in Healthy Male Subjects in a Randomized, Open-Label, Three-Fold Crossover Design (Study 16536)

Study Design

The primary objectives of the study were to investigate the PK dose proportionality of a single oral dose of a 10-mg tablet in comparison to a 20-mg tablet in the fasting condition, and to investigate the effect of a high fat, high calorie meal on the PK after a single oral dose of a 20-mg tablet. Healthy white males aged 18 to 45 years with a BMI of 18 to 29.9 kg/m^2 were included.

Results

Table 106. Point Estimates (LS-Means) and Exploratory 90% CIs for the Ratio of 20 mg Fed/20 mg Fasted of Selected PK Parameters of Finerenone

Parameter	n	Geo. CV (%)	LS-mean	90% CI
AUC	18	12.78	120.90	[112.51 ; 129.91]
C_{max}	18	26.53	81.27	[70.14 ; 94.16]

Source: Applicant, Study 16536, Report PH-39623, Table 2-2.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetics

Table 107. Point Estimates (LS-Means) and Exploratory 90% CIs for the Ratio of 20 mg Fasted/10 mg Fasted of Selected PK Parameters of Finerenone

Parameter	n	Geo. CV (%)	LS-mean	90% CI
AUC	18	12.78	198.86	[185.07 ; 213.68]
AUC/D	18	12.78	99.43	[92.54 ; 106.84]
C_{max}	18	26.53	186.03	[160.55 ; 215.54]
C_{max}/D	18	26.53	93.01	[80.28 ; 107.77]

Source: Applicant, Study 16536, Report PH-39623, Table 2-3.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetics

Reviewer's Comment

There was a food effect on a single oral dose of 20 mg finerenone administered as an IR tablet when taken with a high fat, high calorie meal (Table 106); however, the change in exposure was quite modest. Food resulted in a delayed time to reach peak plasma concentrations. Dose proportionality was confirmed between the 10 mg and 20 mg finerenone IR tablets after single oral doses in the fasted state (Table 107).

Single Center, Randomized, Open-Label, 5-Fold Crossover Study in Healthy Male Subjects to Investigate the Pharmacokinetic Dose Proportionality of BAY 94-8862 Given as 5 Different Single Oral IR Tablet Doses (1.25, 2.5, 5.0, 7.5 and 10 mg) (Study 15481)

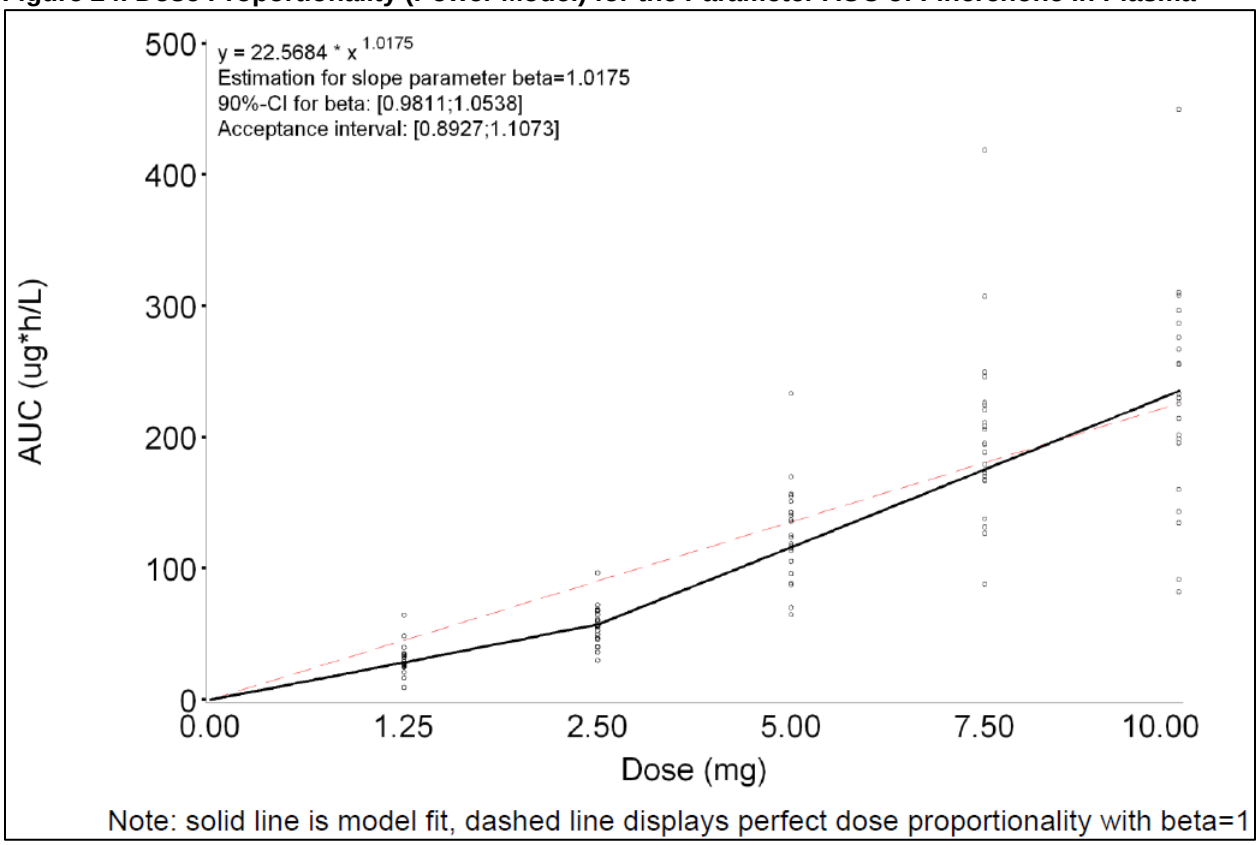
Study Design

The primary objective was to investigate the dose proportionality of finerenone exposure in plasma when given as 1.25, 2.5, 5.0, 7.5 and 10 mg IR tablets under fasting conditions in healthy male subjects. The secondary objective was to assess the safety and tolerability of finerenone at these doses. The participants were healthy white males aged 18 to 46 years with BMIs of 18 to 29.9 kg/m^2.

Results

The primary parameter for the evaluation of the dose proportionality between the highest dose strength of the IR tablet containing 10 mg finerenone and the lowest tablet strength containing 1.25 mg of finerenone was AUC. For AUC, the point estimator for ß was 1.0175. The associated 90% confidence interval of [0.9811, 1.0538] was completely included within the pre-specified relevant range of (0.8927, 1.1073) which was the accepted range to demonstrate dose proportionality. This is shown graphically in Figure 24. For C_{max} and AUC(0-t_{last}), the 90% CIs were [0.9126, 0.9991] and [0.9883, 1.0614], respectively. For both parameters the confidence intervals were contained within the pre-specified range.

Figure 24. Dose Proportionality (Power Model) for the Parameter AUC of Finerenone in Plasma



Source: Applicant, Study 15481, Report PH-37391, Figure 9-3.
Abbreviations: AUC, area under the curve; CI, confidence interval

Reviewer's Comment

Statistical analyses for AUC, C_{max}, and AUC(0-t_{last}) indicate dose proportionality of a single oral dose of finerenone between 1 x 1.25-mg tablet and 8 x 1.25 tablets (10 mg).

Study in Healthy Male Subjects to Assess the Safety, Tolerability and Pharmacokinetics of an Intravenous Solution of Finerenone (Dose Escalation and Group Comparison, Part 1) and to Investigate the absolute Bioavailability of an Oral Dose of 5 mg Finerenone (BAY 94-8862) in Comparison to an Intravenous Solution of Finerenone (Planned Dose 1 mg) Administered Over 1 Hour (Randomized, Non-Blinded, Non-Placebo-Controlled, 2-Way Crossover Design, Part 2) (Study 16535)

Study Design

The objectives of Part 1 with intravenous (IV) finerenone doses, including 0.25 mg,0.5 mg, and 1.0 mg infused over 1 h, were to investigate the safety, tolerability, and PK of these treatments and to select an appropriate IV dose for Part 2. The primary objective of Part 2 of this study, performed in a randomized, non-blinded, non-placebo controlled 2-way crossover design in 16 healthy male subjects, was to evaluate the absolute bioavailability of a single oral dose of a 5 mg IR tablet of finerenone in comparison to an IV infusion of 1 mg over 1 h and to characterize the PK of finerenone after IV administration. The 1 mg IV dose was determined by results from Part 1. Participants were healthy white male subjects aged 18 to 46 years with a BMI of 18 to 29.9 kg/m^2.

Results

Only results from Part 2 of the study are discussed. Oral bioavailability of finerenone from a 5 mg IR tablet compared to an IV dose of 1 mg was calculated to be 43.5%, (95% CI 38.3% to 49.5%); 1.6% of unchanged finerenone and 0.8% of unchanged finerenone were excreted into urine for IV and oral dosing, respectively.

Table 108. Point Estimates and 95% CIs for the Ratio "Finerenone 5 mg Tab/Finerenone 1 mg IV" of Primary PK Parameters of Finerenone and Its Metabolites

Analyte	Parameter	Unit	N	CV(%)	LS-mean	95% CI
Finerenone	AUC/D	h/L	15	16.3	0.4352	[0.3831; 0.4945]
	C_{max}/D	/L	15	20.1	0.4682	[0.3999; 0.5481]
M-1	AUC/D	h/L	15	14.6	1.0022	[0.8934; 1.1242]
	C_{max}/D	/L	15	12.8	1.5067	[1.3622; 1.6666]
M-2	AUC/D	h/L	8	8.10	1.1519	[1.0400; 1.2759]
	C_{max}/D	/L	15	7.76	1.5965	[1.5017; 1.6973]
M-3	C_{max}/D	/L	15	17.9	1.4941	[1.2984; 1.7192]

Source: Applicant, Study 16535, Report PH-38789, Table 9-17.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic; Tab, tablet

Reviewer's Comment

Finerenone was fairly dose proportional with respect to the overall exposure and maximum plasma concentrations of finerenone when administered IV over 0.25 to 1 mg. The oral

bioavailability of finerenone as determined from a 5 mg IR tablet and an IV dose of 1 mg was calculated to be 43.5% (Table 108). Treatments with finerenone were safe and well tolerated when administered IV or as an IR tablet.

Study to Investigate the Effectiveness of Different Single Oral Doses of BAY 94-8862 on Natriuresis After Administration of 0.5 mg Fludrocortisone (Astonin H®) With 50 mg Eplerenone (Inspra®) as Active Control in Healthy Male Subjects in a Randomized, Single-Blind, Placebo-Controlled, Combined 3-Fold Crossover, and Parallel-Group Design (Study 13786)

Study Design

The primary objective was to investigate the effectiveness of single oral doses of finerenone on natriuresis after administration of 0.5 mg fludrocortisone (Astonin H®) in healthy male subjects. The secondary objectives included the assessment of the effect of the active control (50 mg eplerenone – Inspra®) on natriuresis after administration of 0.5 mg fludrocortisone, and the assessment of finerenone and eplerenone PK after single oral doses. There were 5 dose steps: dose step 1 was a 20 mg PEG solution, dose step 2 was a 10 mg PEG solution, dose step 3 was a 5 mg PEG solution, dose step 4 was 2 x 10 mg IR tablets, and dose step 5 was a 2.5 mg PEG solution. Matching placebos were used. Eplerenone was given as a 50-mg dose, and fludrocortisone was given as 5 x 0.1-mg tablets. Participants were healthy white male subjects, aged 18 to 46 years, with a BMI of 18 to 29.9 kg/m^2. PD parameters included blood pressure and heart rate; urine markers including urinary volume, sodium, potassium, magnesium, calcium, creatinine; ratios of urinary sodium/creatinine, urinary potassium/creatinine, urinary sodium/potassium, the log10 of urinary sodium/potassium ratio, and log10 (10*urinary sodium/potassium ratio); and exploratory biomarkers including plasma renin activity, serum aldosterone, and pharmacodynamic mRNA expression of mineralocorticoid receptor (MR) regulated genes. Primary PK parameters for both finerenone and eplerenone included AUC and C_{max}.

Results

Table 109. LS-Means for the Difference of Finerenone/Eplerenone for the Parameter Sodium (mmol/L) in Urine

Dose Step (Treatment)	02H00M-10H00M	02H00M-06H00M	06H00M-10H00M	10H00M-14H00M	14H00M-18H00M	18H00M-22H00M	22H00M-26H00M
5 (2.5 mg sol)	-10.68*	-6.24	-15.86*	-3.25	-5.42	1.17	3.58
3 (5 mg sol)	-22.79*	-17.00*	-34.98*	-28.99*	-22.88	-8.72	-9.62
2 (10 mg sol)	3.67	5.50	-1.33	-3.18	-3.75	-6.75	2.53
1 (20 mg sol)	10.22*	12.68*	-6.38	-5.48	-16.04	-4.82	2.31
4 (2x10 mg tab)	1.58	0.33	10.75*	-1.25	5.17	-9.42	-1.25

Source: Applicant, Study 13786 Report, Table 9-3.
Abbreviations: LS-mean, least squares mean

Table 110. LS-Means for the Ratio of Finerenone/Eplerenone for the Parameter log10(10*Na/K)

Dose Step (Treatment)	02H00M-10H00M	02H00M-06H00M	06H00M-10H00M	10H00M-14H00M	14H00M-18H00M	18H00M-22H00M	22H00M-26H00M
5 (2.5 mg sol)	0.58*	0.71*	0.39*	0.67*	0.97	1.17	1.02
3 (5 mg sol)	0.55*	0.70*	0.38*	0.56*	0.70*	0.74*	0.89
2 (10 mg sol)	0.92	1.15	0.64*	0.55*	0.79*	0.79*	1.04
1 (20 mg sol)	1.35*	1.64*	0.87	0.73*	0.65*	0.76*	1.03
4 (2x10 mg tab)	1.53*	1.73*	1.68*	1.03	0.84*	0.85	0.90

Source: Applicant, Study 13786 Report, Table 9-9.
Abbreviations: LS-mean, least squares mean

Reviewer's Comment

Neither finerenone nor eplerenone affected blood pressure, heart rate, or neurohormones. Finerenone showed natriuretic effects (log10(10xNa/K ratio)) at all doses that were tested (Table 110). 20 mg of finerenone in either the PEG solution or as 2 x 10-mg tablets was more effective in increasing natriuresis compared to eplerenone administered as a 50-mg dose. Fludrocortisone had a significant effect on mRNA parameters; however, these changes were not influenced by treatment with either finerenone or eplerenone. There were no significant PK findings in this study.

Study to Investigate the Influence of Age and Gender on the Pharmacokinetics of a Single Oral Dose of a 10 mg BAY 94-8862 IR Tablet in a Randomized, Single-Blind, Placebo-Controlled, Group-Comparison Design in Healthy Male and Female Subjects (Study 14508)

Study Design

The primary objective of the study was to investigate the influence of age and gender on the pharmacokinetics of finerenone given as a 10 mg IR tablet as a single dose in young and elderly healthy male and female subjects (of nonchildbearing potential). Secondary objectives were to assess the safety and tolerability of finerenone. Participants were healthy subjects assigned to 1 of 4 age and gender groups (young men aged 18 to 45 years, elderly male subjects aged 65 to 80 years with approximately 4 to 6 subjects aged ≥73 years, as well as young and elderly women (same age limits as for men). PD parameters included heart rate over 1 min and neurohormones (plasma renin activity, angiotensin II, and aldosterone). PK parameters were derived from the plasma concentration versus time profiles of finerenone and the M-1, M-2, and M-3 metabolites.

Results

Table 111. Point Estimators (LS-Means) and 2-Sided 90% CIs of Selected PK Parameters After Administration of Finerenone by Sex

Analyte	Ratio	Parameter	n	CV	Estimated ratio (%)	90% confidence interval (%)
BAY 94-8862	Elderly men / young men	AUC	18	28	120.30	[96.33 ; 150.24]
		AUC_{norm}	18	27	117.36	[94.63 ; 145.54]
		C_{max}	18	34	124.42	[95.72 ; 161.72]
		$C_{max, norm}$	18	31	121.37	[95.31 ; 154.56]
	Elderly women / young women	AUC	18	28	149.35	[119.59 ; 186.52]
		AUC_{norm}	18	27	136.78	[110.29 ; 169.63]
		C_{max}	18	34	183.46	[141.15 ; 238.46]
		$C_{max, norm}$	18	31	168.02	[131.94 ; 213.96]
	Young women / young men	AUC	18	28	100.72	[80.65 ; 125.78]
		AUC_{norm}	18	27	86.99	[70.15 ; 107.88]
		C_{max}	18	34	85.10	[65.47 ; 110.61]
		$C_{max, norm}$	18	31	73.50	[57.72 ; 93.60]
	Elderly women / elderly men	AUC	18	28	125.04	[100.12 ; 156.16]
		AUC_{norm}	18	27	101.39	[81.76 ; 125.74]
		C_{max}	18	34	125.48	[96.54 ; 163.10]
		$C_{max, norm}$	18	31	101.75	[79.90 ; 129.57]

Source: Applicant, Study 14508, Report PH-36801, Table 2-3.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Table 112. Point Estimators (LS-Means) and 2-Sided 90% CIs of Selected PK Parameters After Administration of Finerenone Combined

Analyte	Ratio	Parameter	n	CV	Estimated ratio (%)	90% confidence interval (%)
BAY 94-8862	Elderly / young	AUC	36	28	134.04	[114.55 ; 156.85]
		AUC_{norm}	36	27	126.70	[108.81 ; 147.52]
		C_{max}	36	34	151.08	[125.51 ; 181.86]
		$C_{max, norm}$	36	31	142.80	[120.37 ; 169.42]

Source: Applicant, Study 14508, Report PH-36801, Table 2-4.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Reviewer's Comment

Finerenone did not exert relevant effects in healthy subjects on the PD parameters heart rate over 1 min, blood pressure, and on neurohormones. The increase in finerenone exposure in elderly subjects ≥65 years was 34% and 50% for geometric mean AUC and C_{max}, respectively, compared to young subjects ≤45 years. When normalized for body weight, these differences were smaller, with AUC_{norm} 27% higher in the elderly and $C_{max,norm}$ 43% higher in the elderly (Table 111 and Table 112).

Investigation of Pharmacokinetics, Safety, and Tolerability of BAY 94-8862 in Male and Female Subjects With Renal Impairment and in Age- and Weight-Matched Healthy Subjects Following a Single Oral Dose of 10 mg BAY 94-8862 IR Tablet in a Single-Center, Non-Randomized, Non-Controlled, Non-Blinded, Observational Study With Group Stratification (Study 14509)

Study Design

The primary objective of the study was to evaluate the PK of finerenone and its metabolites M-1, M-2, and M-3 after a single oral dose of a 10 mg finerenone IR tablet in subjects with mild to severe renal impairment, stratified according to creatinine clearance [subjects with creatinine clearance (CL_{CR}) 50 to 80 mL/min (8 subjects), 30 - <50 mL/min (8 subjects), and <30 mL/min (8 subjects)] determined 2 to 14 days prior to dosing, with age-, weight-, and gender-matched healthy subjects [8 healthy subjects with CL_{CR} >80 mL/min]. The secondary objectives were to assess safety, tolerability, and PD of finerenone. Participants were men and women aged 18 to 79 years with a BMI between 18 and 34 kg/m^2. PD parameters included plasma renin activity, plasma angiotensin II, serum aldosterone, plasminogen activator inhibitor-1, urinary volume, urinary creatinine, and the urinary electrolytes sodium, potassium, and magnesium as well as ratios thereof. Both plasma and urine PK parameters were collected for finerenone and M-1, M-2, and M-3 metabolites.

Results

PK parameters for finerenone in those with renal impairment are shown below in Table 113 to Table 116.

Table 113. PK Parameters of Finerenone in Plasma and Urine After a Single Oral Dose of a 10 mg Immediate Release Tablet Excluding an Outlier in the Moderate Renal Impairment Group

Parameter	Unit	Normal renal function (healthy subjects) CL_{CR} >80 mL/min n=8	Mild renal impairment CL_{CR} 50 - 80 mL/min n=8	Moderate renal impairment CL_{CR} 30 - <50 mL/min n=7	Severe renal impairment CL_{CR} <30 mL/min n=9
Plasma					
AUC	µg*h/L	218/25.9 (138-296)	221/58.7 (88.1-440)	352/57.8 (114-567)	317/83.3 (60.0-773)
AUC_{norm}	kg*h/L	1.76/28.3 (1.20-2.66)	1.65/58.8 (0.669-3.17)	2.79/58.7 (1.01-4.71)	2.54/97.5 (0.408-5.87)
AUC/D	$(h/L)*10^{-3}$	21.8/25.9 (13.8-29.6)	22.1/58.7 (8.81-44.0)	35.2/57.8 (11.4-56.7)	31.7/83.3 (6.00-77.3)
$AUC(0\text{-}t_{last})$	µg*h/L	217/25.9 (138-295)	219/58.5 (87.5-435)	350/58.0 (113-565)	315/83.9 (59.0-771)
C_{max}	µg/L	95.5/32.3 (67.4-146)	105/49.1 (58.3-235)	110/45.2 (51.8-170)	88.4/58.1 (24.7-166)
$C_{max,norm}$	kg/L	0.772/32.4 (0.512-1.20)	0.785/55.5 (0.355-1.55)	0.873/38.6 (0.456-1.41)	0.710/66.8 (0.168-1.40)
C_{max}/D	$(1/L)*10^{-3}$	9.55/32.3 (6.74-14.6)	10.5/49.1 (5.83-23.5)	11.0/45.2 (5.18-17.0)	8.84/58.1 (2.47-16.6)
t_{max}[a]	h	0.625 (0.500-2.00)	0.625 (0.500-3.00)	0.500 (0.500-0.750)	0.750 (0.500-4.00)
$t_{1/2}$	h	2.21/14.7 (1.89-2.76)	2.26/29.2 (1.32-3.47)	2.80/25.5 (1.83-3.53)	2.78/45.8 (1.28-4.56)
MRT	h	2.85/19.1 (2.29-4.15)	2.94/36.3 (2.24-6.65)	3.51/28.3 (2.29-4.53)	3.87/37.5 (2.48-6.62)
CL/F	L/h	45.9/25.9 (33.8-72.4)	45.3/58.7 (22.7-114)	28.4/57.8 (17.6-87.4)	31.6/83.3 (12.9-167)
V_z/F	L	146/25.1 (94.3-201)	148/39.9 (92.0-322)	115/43.0 (80.0-265)	127/44.8 (79.0-308)
Urine					
$A_{E,ur}$[b]	µg	81.0/30.8 (39.3-128)	48.2/22.9 (23.4-85.1)	57.2/30.2 (6.06-95.2)	37.5/22.0 (7.94-65.9)
$\%A_{E,ur}$[b]	%	0.810/0.308 (0.393-1.28)	0.482/0.229 (0.234-0.851)	0.572/0.302 (0.0606-0.952)	0.375/0.220 (0.0794-0.659)
CL_R	L/h	0.347/21.4 (0.284-0.484)	0.197/53.1 (0.0721-0.326)	0.128/54.0 (0.0530-0.245)	0.0931/121.1 (0.0156-0.190)

Source: Applicant, Study 14509, Report PH-36810, Table 2-3.
[a] Median (range)
[b] Arithmetic mean/SD (range)
Abbreviations: AUC, area under the curve; CL, clearance; CR, creatinine; MRT, mean residence time; PK, pharmacokinetic

Table 114. PK Parameters of Unbound Finerenone in Plasma After a Single Oral Dose of a 10 mg Immediate Release Tablet Excluding an Outlier in the Moderate Renal Impairment Group

Parameter	Unit	Normal renal function (healthy subjects) CL_{CR} >80 mL/min n=8	Mild renal impairment CL_{CR} 50 - 80 mL/min n=8	Moderate renal impairment CL_{CR} 30 - <50 mL/min n=7	Severe renal impairment CL_{CR} <30 mL/min n=9
AUC_u	µg*h/L	23.0/23.5 (16.4-30.3)	22.8/55.9 (9.21-45.8)	36.1/60.2 (11.5-61.7)	33.7/78.7 (6.81-78.0)
$AUC_{u,norm}$	kg*h/L	0.186/26.4 (0.142-0.280)	0.170/54.8 (0.0700-0.330)	0.286/62.9 (0.101-0.512)	0.270/92.4 (0.0463-0.593)
$C_{max,u}$	µg/L	10.1/31.6 (7.35-15.5)	10.8/44.4 (6.23-22.1)	11.3/44.4 (5.19-18.5)	9.40/53.9 (2.81-17.4)
$C_{max,u,norm}$	kg/L	0.0815/32.0 (0.0559-0.127)	0.0810/50.1 (0.0398-0.148)	0.0897/40.0 (0.0457-0.153)	0.0755/62.2 (0.0191-0.147)
CL_u/F	L/h	435/23.5 (330-611)	439/55.9 (218-1090)	277/60.2 (162-873)	297/78.7 (128-1470)
f_u	%	10.6/6.4 (9.41-11.9)	10.3/5.8 (9.43-11.2)	10.3/7.1 (9.03-11.0)	10.6/6.3 (9.62-11.4)

Source: Applicant, Study 14509, Report PH-36810, Table 2-4.
Exposure to the inactive metabolites M-1, M-2, and M-3 was increased in renal impairment. These results are shown below in Table 78.
Abbreviations: AUC, area under the curve; CL, clearance; CR, creatinine; PK, pharmacokinetic; Fu, fraction unbound

Table 115. PK Parameters of Finerenone Metabolites M-1, M-2, and M-3 in Plasma After a Single Oral Dose of a 10 mg Immediate Release Tablet

Parameter	Unit	Participants with CL_{CR} > 80 mL/min n=8	Participants with CL_{CR} 50-80 mL/min n=8	Participants with CL_{CR} 30- <50 mL/min n=7	Participants with CL_{CR} < 30 mL/min n=9
M-1					
AUC	µg*h/L	1220	1270	2556	2052
C_{max}	µg/L	159	165	182	136
t_{max}	h	0.750	1	2	2.5
$t_{1/2}$	h	10.5	11.7	19.7	20.7
M-2					
AUC	µg*h/L	594	702	1060	1132
C_{max}	µg/L	47.1	56.1	49.5	47.7
t_{max}	h	4	3.26	8	8
$t_{1/2}$	h	6.18	7.51	13.1	14.2
M-3					
AUC	µg*h/L	301	442	1114	1727
C_{max}	µg/L	20.2	29.8	39.6	47.8
t_{max}	h	6	6	12	16
$t_{1/2}$	h	5.68	5.91	12.36	16.3

Source: Table created by reviewer from data in Study 14509, Report PH-36810
Abbreviations: AUC, area under the curve; CL, clearance; CR, creatinine; PK, pharmacokinetic
.

The LS-mean %-ratio for AUC and C_{max} in those with mild, moderate, and severe renal impairment compared to normal renal function excluding and including an outlier in the moderate renal impairment group are shown below in Table 117 for unbound finerenone.

Table 116. Point Estimators (LS-means) and 2-Sided 90% CIs for PK Parameters of Finerenone in Plasma After a Single Oral Dose of a 10 mg Immediate Release Tablet Excluding an Outlier in the Moderate Renal Impairment Group

Ratio	Parameter	Unit	n	CV	Estimated ratio (%)	90% confidence interval (%)
Mild renal impairment / normal renal function	AUC	µg*h/L	8/8	59	101.19	[63.38 ; 161.57]
	AUC_{norm}	kg*h/L	8/8	64	93.69	[56.74 ; 154.72]
	C_{max}	µg/L	8/8	47	109.74	[74.90 ; 160.78]
	$C_{max, norm}$	kg/L	8/8	51	101.60	[67.74 ; 152.39]
Moderate renal impairment normal renal function	AUC	µg*h/L	7/8	59	161.41	[99.45 ; 261.98]
	AUC_{norm}	kg*h/L	7/8	64	158.11	[94.07 ; 265.73]
	C_{max}	µg/L	7/8	47	115.39	[77.70 ; 171.34]
	$C_{max, norm}$	kg/L	7/8	51	113.02	[74.29 ; 171.95]
Severely impaired / normal renal function	AUC	µg*h/L	9/8	59	145.37	[92.26 ; 229.06]
	AUC_{norm}	kg*h/L	9/8	64	144.31	[88.63 ; 234.97]
	C_{max}	µg/L	9/8	47	92.56	[63.86 ; 134.17]
	$C_{max, norm}$	kg/L	9/8	51	91.89	[61.97 ; 136.26]

Source: Applicant, Study 14509, Report PH-36810, Table 2-8.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Table 117. Point Estimators (LS-means) and 2-Sided 90% CIs for Selected PK Parameters of Unbound Finerenone in Plasma after a Single Oral Dose of a 10 mg Immediate Release Tablet Excluding an Outlier in the Moderate Renal Impairment Group

Ratio	Parameter	Unit	n	CV	Estimated ratio (%)	90% confidence interval (%)
Mild renal impairment / normal renal function	AUC_u	µg*h/L	8/8	57	98.94	[62.81 ; 155.85]
	$AUC_{u,norm}$	kg*h/L	8/8	63	91.61	[56.19 ; 149.36]
	$C_{max,u}$	µg/L	8/8	44	107.29	[74.76 ; 153.98]
	$C_{max,u,norm}$	kg/L	8/8	48	99.34	[67.55 ; 146.09]
Moderate renal impairment normal renal function	AUC_u	µg*h/L	7/8	57	157.11	[98.16 ; 251.45]
	$AUC_{u,norm}$	kg*h/L	7/8	63	153.89	[92.78 ; 255.24]
	$C_{max,u}$	µg/L	7/8	44	112.31	[77.27 ; 163.24]
	$C_{max,u,norm}$	kg/L	7/8	48	110.01	[73.80 ; 163.98]
Severely impaired / normal renal function	AUC_u	µg*h/L	9/8	57	146.51	[94.21 ; 227.84]
	$AUC_{u,norm}$	kg*h/L	9/8	63	145.44	[90.44 ; 233.88]
	$C_{max,u}$	µg/L	9/8	44	93.29	[65.67 ; 132.53]
	$C_{max,u,norm}$	kg/L	9/8	48	92.61	[63.66 ; 134.72]

Renal function groups according to EMA guidance[7]
Source: Applicant, Study 14509, Report PH-36810, Table 2-9.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Reviewer's Comment

A single oral dose of finerenone did not exert relevant effects in any of the 4 renal function groups on plasma renin activity, plasma angiotensin II, serum aldosterone, or plasminogen activator inhibitor-1. There were also no clinically relevant differences between renal function

groups in any of the measured urine electrolyte parameters after a single oral dose. Compared to those with CL_{CR} >80 mL/min, those with a CL_{CR} 50 to 80 mL/min did not have much of a change in AUC or AUC_u, with an estimated ratio % for mild renal impairment/normal renal function of 101% and 99%, respectively. Compared to those with CL_{CR} >80 mL/min, those with a CL_{CR} 30- <50 mL/min had an increase in AUC and AUC_u, with an estimated ratio % for mild renal impairment/normal renal function of 161% and 157%, respectively. Compared to those with CL_{CR} >80 mL/min, those with a CL_{CR} <30 mL/min had an increase in AUC and AUC_u, with an estimated ratio % for mild renal impairment/normal renal function of 145% and 147%, respectively. The extent of the change in exposure remained similar across renal function groups regardless of total or unbound finerenone.

Exposure to the inactive metabolites M-1, M-2, and M-3 was increased in renal impairment. In those with a CL_{CR} 50 to 80 mL/min, AUCs increased to 104%, 118%, and 147% of those with a CL_{CR} >80 mL/min for M-1, M-2, and M-3, respectively. In those with a CL_{CR} 30-<50 mL/min, AUCs increased to 209%, 178%, and 370% of those with a CL_{CR} >80 mL/min for M-1, M-2, and M-3, respectively. In those with a CL_{CR} <30 mL/min, AUCs increased to 168%, 190%, and 575% of those with a CL_{CR} >80 mL/min for M-1, M-2, and M-3, respectively. C_{max} data were variable between renal impairment groups.

Investigation of the Pharmacokinetics, Safety, and Tolerability of Finerenone (BAY 94-8862) in Subjects With Hepatic Impairment (Classified as Child Pugh A or B) and in Age-, Weight-, and Gender-Matched Healthy Subjects Following a Single Oral Dose in a Single-Center, Non-Randomized, Non-Controlled, Non-Blinded, Observational Study With Group Stratification (Study 14510)

Study Design

The primary objective was to evaluate the PK of finerenone following a single oral dose in subjects with mild to moderate hepatic impairment, stratified according to the Child Pugh classification grade A or B, and age-, weight- and gender- matched healthy subjects. The secondary objective of this study was to evaluate safety and tolerability of finerenone. A single dose of 5 mg finerenone was administered. Participants were white subjects 18 to 79 years of age with a BMI of 18 to 34 kg/m^2. Participants had mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment. Other participants were age-, weight-, and gender-matched healthy subjects.

Results

Table 118. PK Parameters of Total and Unbound Finerenone in Plasma Following a Single Dose Administration of 5 mg (Geometric Mean/CV% [Range])

Parameter	Unit	Child Pugh A N=9	Child Pugh B N=9	Healthy subjects N=9
AUC	µg·h/L	118/52.5 (52.8 - 253)	150 /31.1 (88.4 - 214)	108/18.3 (90.5 - 146)
AUC_{norm}	kg·h/L	1.98/44.7 (0.927 - 3.14)	2.45/43.4 (1.39 - 4.50)	1.84/18.7 (1.36 - 2.43)
AUC_u	µg·h/L	13.0/53.4 (5.33 - 29.1)	19.3/25.0 (12.6 - 25.9)	12.4/24.1 (8.56 - 18.4)
C_{max}	µg/L	45.9/47.0 (19.5 - 102)	47.2/33.6 (27.9 - 72.4)	47.6/26.3 (34.5 - 73.4)
$C_{max,norm}$	kg/L	0.773/39.2 (0.343 - 1.27)	0.772/27.0 (0.497 - 1.13)	0.807/25.3 (0.588 - 1.28)
$C_{max,u}$	µg/L	5.09/50.7 (1.97 - 11.8)	6.07/38.7 (3.74 - 10.6)	5.46/28.5 (3.64 - 8.14)
$t_{1/2}$	h	2.71/15.5 (2.21 - 3.52)	3.18/34.1 (1.95 - 5.56)	2.29/8.69 (1.97 - 2.69)
t_{max}[a]	h	0.500 (0.50-1.00)	0.500 (0.25-2.50)	0.750 (0.50-1.00)
f_u	%	11.1/6.60 (9.90 - 12.2)	12.9/15.9 (9.93 - 17.7)	11.5/9.86 (9.12 - 12.6)

a median and range

Source: Applicant, Study 14510, Report PH-38432, Table 2-1.
Abbreviations: AUC, area under the curve; CV, coefficient of variation; PK, pharmacokinetic

Table 119. Point Estimates and 90% CIs for Ratios of PK Parameters of Total and Unbound Finerenone

Parameter	Geo. %CV	Ratio	LS-mean	90% CI
AUC	36.2	CP-A/healthy subjects	1.0838	[0.8169; 1.4379]
		CP-B/healthy subjects	1.3827	[1.0422; 1.8344]
AUC_{norm}	37.2	CP-A/healthy subjects	1.0765	[0.8052; 1.4394]
		CP-B/healthy subjects	1.3354	[0.9988; 1.7855]
C_{max}	36.4	CP-A/healthy subjects	0.9643	[0.7256; 1.2816]
		CP-B/healthy subjects	0.9910	[0.7457; 1.3172]
$C_{max,norm}$	31.0	CP-A/healthy subjects	0.9579	[0.7502; 1.2229]
		CP-B/healthy subjects	0.9572	[0.7497; 1.2221]
AUC_u	36.1	CP-A/healthy subjects	1.0472	[0.7894; 1.3892]
		CP-B/healthy subjects	1.5517	[1.1697; 2.0584]
$C_{max,u}$	40.1	CP-A/healthy subjects	0.9318	[0.6825; 1.2720]
		CP-B/healthy subjects	1.1122	[0.8147; 1.5183]
f_u	11.4	CP-A/healthy subjects	0.9662	[0.8814; 1.0592]
		CP-B/healthy subjects	1.1222	[1.0237; 1.2302]

Source: Applicant, Study 14510, Report PH-38432, Table 2-2.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Table 120. Point Estimates and 90% CIs for Ratios of PK Parameters of M-1

Parameter	Geo. %CV	Ratio	LS-mean	90% CI
AUC	41.5	CP-A/healthy subjects	1.0674	[0.7738; 1.4724]
		CP-B/healthy subjects	1.1093	[0.8042; 1.5302]
AUC_{norm}	41.2	CP-A/healthy subjects	1.0602	[0.7705; 1.4590]
		CP-B/healthy subjects	1.0714	[0.7786; 1.4743]
C_{max}	37.7	CP-A/healthy subjects	0.8204	[0.6116; 1.1005]
		CP-B/healthy subjects	0.6775	[0.5051; 0.9088]
$C_{max,norm}$	30.7	CP-A/healthy subjects	0.8149	[0.6396; 1.0383]
		CP-B/healthy subjects	0.6544	[0.5136; 0.8338]

Source: Applicant, Study 14510, Report PH-38432, Table 9-12.
Abbreviations: AUC, area under the curve; CI, confidence interval; CP, Child Pugh; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Table 121. Point Estimates and 90% CIs for Ratios of PK Parameters of M-2

Parameter	Geo. %CV	Ratio	LS-mean	90% CI
AUC	26.1	CP-A/healthy subjects	1.4784	[1.2023; 1.8180]
		CP-B/healthy subjects	1.7724	[1.4413; 2.1795]
AUC_{norm}	25.2	CP-A/healthy subjects	1.4685	[1.2022; 1.7938]
		CP-B/healthy subjects	1.7118	[1.4014; 2.0910]
C_{max}	27.2	CP-A/healthy subjects	1.2045	[0.9711; 1.4940]
		CP-B/healthy subjects	1.1380	[0.9175; 1.4114]
$C_{max,norm}$	15.8	CP-A/healthy subjects	1.1964	[1.0545; 1.3575]
		CP-B/healthy subjects	1.0991	[0.9687; 1.2470]

Source: Applicant, Study 14510, Report PH-38432, Table 9-13.
Abbreviations: AUC, area under the curve; CI, confidence interval; CP, Child Pugh; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Table 122. Point Estimates and 90% CIs for Ratios of PK Parameters of M-3

Parameter	Geo. %CV	Ratio	LS-mean	90% CI
AUC[a]	50.8	CP-A/healthy subjects	1.0679	[0.7164; 1.5919]
		CP-B/healthy subjects	1.2564	[0.8429; 1.8729]
AUC_{norm}[a]	46.6	CP-A/healthy subjects	1.0527	[0.7275; 1.5231]
		CP-B/healthy subjects	1.2042	[0.8323; 1.7423]
C_{max}	67.3	CP-A/healthy subjects	0.9045	[0.5525; 1.4810]
		CP-B/healthy subjects	0.8987	[0.5489; 1.4714]
$C_{max,norm}$	60.7	CP-A/healthy subjects	0.8985	[0.5718; 1.4118]
		CP-B/healthy subjects	0.8680	[0.5523; 1.3639]

a for AUC and AUC_{norm} N=26 including 9 CP-A and CP-B and 8 healthy subjects
Source: Applicant, Study 14510, Report PH-38432, Table 9-14.
Abbreviations: AUC, area under the curve; CI, confidence interval; CP, Child Pugh; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Reviewer's Comment

Clearance was reduced in those with moderate hepatic impairment when compared to healthy subjects, increasing AUC and AUC_u by 38% and 55%, respectively. Hepatic impairment status had minimal effect on C_{max} and $C_{max,u}$. Mild hepatic impairment did not affect C_{max} or AUC, either total or unbound. The fu was slightly decreased in those with mild hepatic impairment

with an LS-mean ratio of 0.97, and slightly increased in those with moderate hepatic impairment with an LS-mean ratio of 1.12; however, the 90% CI fell within 0.8 to 1.25, indicating that the fu was fairly similar regardless of hepatic function (Table 119).

In the mild and moderate hepatic impairment groups, there was an 18% and 32% reduction in M-1 C_{max}; however, overall exposure of M-1 was similar across subjects regardless of liver impairment (Table 120). Overall exposure to M-2 was increased, with AUC values 48% and 77% higher in those with mild and moderate hepatic impairment, respectively. C_{max} was not affected by impaired liver function for M-2 (Table 121). For M-3, there was a higher trend for AUC and C_{max} in hepatically impaired subjects (Table 122).

Randomized, Non-Blinded, Non-Placebo-Controlled, 2-Way Cross-Over Study to Investigate the Influence of Multiple Doses of 500 mg Erythromycin TID on the Safety, Tolerability, Pharmacodynamics, and Pharmacokinetics of a Single Oral Dose of 1.25 mg BAY 94-8862 in Comparison to a Single Dose of 1.25 mg of BAY 94-8862 Alone in Healthy Male Subjects (Study 14504)

Study Design

The primary objective was to investigate the influence of multiple oral doses of 500 mg erythromycin TID on the safety, tolerability, pharmacodynamics, and pharmacokinetics of 1.25 mg BAY 94-8862 given as a single oral dose in comparison to 1.25 mg BAY 94-8862 given alone. Participants were healthy white male subjects 18 to 46 years of age with BMIs of 18 to 29.9 kg/m^2. This was a 2-way cross-over study. In Treatment A, a single oral dose of a 1.25 mg finerenone IR tablet was given in the fasted state. In Treatment B, from -4 Days to -0 Days 8H, 500 mg of erythromycin was administered as 1 x 500-mg tablets TID, followed by a 1.25 mg finerenone IR tablet given in the fasted state after the 4-day erythromycin pre-treatment. There was a wash-out period of at least 7 days between each period. PK of finerenone and the metabolites were measured.

Results

Table 123. Point Estimates (LS-Means) and 2-Sided 90% CIs for the Ratios of AUC, AUC(0-t_{last}), and C_{max} of Finerenone

Analyte/ ratio	Parameter	n	Estimated ratio (%)	90% confidence interval (%)
BAY 94-8862 1.25 mg IR tablet + erythromycin / BAY 94-8862 1.25 mg IR tablet alone	AUC	15	348.2	[301.7; 401.9]
	AUC(0-t_{last})	15	350.7	[304.3; 404.3]
	C_{max}	15	188.2	[163.1; 217.2]

Source: Applicant, Study 14504, Report PH-37055, Table 2-2.
Abbreviations: AUC, area under the curve; CI, confidence interval; IR, immediate-release; LS-mean, least squares mean

Table 124. Point Estimates (LS-Means) and 2-Sdied 90% CIs for the Ratios of AUC, AUC(0-t_{last}), and C_{max} of Finerenone Metabolites

Analyte/ ratio	Parameter	n	Estimated ratio (%)	90% confidence interval (%)
M1 (BAY 1040818)				
BAY 94-8862 1.25 mg IR tablet +	AUC	15	246.3	[218.8; 277.2]
erythromycin /	AUC(0-t_{last})	15	251.5	[224.0; 282.4]
BAY 94-8862 1.25 mg IR tablet alone	C_{max}	15	86.2	[82.51; 90.08]
M2 (BAY 1088089)				
BAY 94-8862 1.25 mg IR tablet +	AUC	7	130.8	[116.0; 147.3]
erythromycin /	AUC(0-t_{last})	15	124.7	[114.4; 136.0]
BAY 94-8862 1.25 mg IR tablet alone	C_{max}	15	51.95	[46.63; 58.01]
M3 (BAY 1088090)[a]				
BAY 94-8862 1.25 mg IR tablet +	AUC(0-t_{last})	10	18.07	[11.07; 29.49]
erythromycin /	C_{max}	10	27.3	[24.03; 30.97]
BAY 94-8862 1.25 mg IR tablet alone				

Source: Applicant, Study 14504, Report PH-37055, Table 9-6.
[a]AUC could not be calculated in any subject receiving concomitant treatment
Abbreviations: AUC, area under the curve; CI, confidence interval; IR, immediate-release; LS-mean, least squares mean

Reviewer's Comment

Pre-administration (500 mg TID for 4 days) and concomitant administration of erythromycin with a single dose of finerenone 1.25-mg tablet on the 5th day led to a 3.5-fold increase in AUC and 1.9-fold increase in finerenone C_{max} (Table 123).

Metabolic transformation of finerenone to M-1 is catalyzed by CYP3A4, as is the subsequent conversion of M-1 to M-2 and of M-2 to M-3. Both M-1 and M-2 had a reduction in C_{max} by 14% and 48%, respectively, indicated by a delayed median t_{max}. There were prolonged half-lives, and an increase in AUC(0-t_{last}) of M-1 and M-2 by 150% and 25%, respectively. M-3 had a reduction in overall exposure, with a 73% decrease in C_{max} and 82% reduction in AUC (Table 124). These results indicate that the PK of finerenone and its metabolites are affected by moderate CYP3A4 inhibitors.

Non-Blind, Non-Placebo-Controlled Study With 2 Treatments in Fixed Sequence to Investigate the Effect of Verapamil (240 mg Controlled-Release Tablet) on the Pharmacokinetics of a Single Dose of Finerenone (5 mg) and to Investigate the Safety and Tolerability of the Combined Administration in Healthy Male Subjects (Study 16910)

Study Design

The primary objective of this study was to investigate the influence of multiple oral doses of verapamil 240 mg once-daily on the pharmacokinetics of 5 mg finerenone given as a single oral dose in comparison to 5 mg finerenone given alone. The secondary objectives were to assess the safety and tolerability of the combined administration of both drugs. Participants were healthy white male subjects between 18 and 45 years and a BMI of 18 to 29.9 kg/m^2. There were 2 treatments in the sequence (Treatment A and Treatment B), and there was no washout between the two treatments. For treatment A, there was a single oral administration of a 5 mg finerenone IR tablet in the morning of Day 1. In Treatment B, volunteers who had electrocardiographic and vital sign responses within acceptable limits and no tolerability issues after single-dose

administration of 120 mg verapamil IR tablet on Day -3 received 240 mg verapamil controlled-release tablet once daily on Days -2, -1, and 1 in the morning. On Day 1, a single oral dose of 5 mg finerenone IR tablet was administered 6 hours after the dose of verapamil.

Results

$AUC_{(0-t)}$ for finerenone and M-1 were increased with verapamil administration. $AUC_{(0-t)}$ was roughly similar for M-2. $AUC_{(0-t)}$ for M-3 was decreased with verapamil administration. While C_{max} was increased for finerenone, C_{max} was reduced for M-1, M-2, and M-3 (Table 125).

Table 125. Point Estimates, 90% CIs, and 2-Sided Prediction Intervals for Selected PK Parameters

	Parameter	CV	Estimated ratio (%)	90% confidence interval (%)	95% prediction interval (%)
Finerenone	AUC	15	270.34	[242.95 ; 300.82]	[165.85 ; 440.68]
	$AUC(0\text{-}t_{last})$	15	270.50	[243.08 ; 301.01]	[165.91 ; 441.01]
	C_{max}	24	222.28	[188.47 ; 262.16]	[104.50 ; 472.82]
BAY 1040818	$AUC(0\text{-}t_{last})$	13	170.54	[155.93 ; 186.52]	[113.22 ; 256.88]
	C_{max}	16	83.64	[74.69 ; 93.66]	[49.85 ; 140.35]
BAY 1088089	$AUC(0\text{-}t_{last})$	14	104.34	[94.33 ; 115.40]	[65.79 ; 165.46]
	C_{max}	12	71.61	[65.67 ; 78.09]	[48.18 ; 106.42]
BAY 1088090	$AUC(0\text{-}t_{last})$	16	48.23	[43.18 ; 53.88]	[29.08 ; 80.01]
	C_{max}	15	38.48	[34.78 ; 42.58]	[24.23 ; 61.12]

Source: Applicant, Study 16910, Report PH-38891, Table 2-1.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; PK, pharmacokinetic

Reviewer's Comment

Verapamil administration as a 240 mg controlled-release tablet at steady-state led to a 2.7 and 2.2-fold increase of finerenone AUC and C_{max} when given concomitantly. For metabolite M-1, the AUC estimated ratio was about 170%, and C_{max} was reduced by 16%. For M-2, $AUC(0\text{-}t_{last})$ was not affected, but C_{max} was reduced by 29%. For M-3, both the $AUC(0\text{-}t_{last})$ and C_{max} decreased by 52 and 61%. This indicates that finerenone is affected by moderate CYP3A4 inhibitors.

Randomized, Non-Blinded, Non-Placebo-Controlled, Two-Way Crossover Study to Investigate the Influence of Multiple Doses of 600 mg Gemfibrozil Twice-Daily on the Pharmacokinetics, Safety and Tolerability of a Single Oral Dose of 10 mg Finerenone in Comparison to a single Dose of 10 mg Finerenone Alone in Healthy Male Subjects (Study 15112)

Study Design

The primary objective of the study was to investigate the influence of multiple oral doses of gemfibrozil 600 mg BID on the pharmacokinetics of 10 mg finerenone. The secondary objective was to assess the safety and tolerability of 10 mg finerenone given as a single oral dose on the background of gemfibrozil in comparison to 10 mg finerenone given alone. Participants were healthy white male subjects between 18 and 45 years with a BMI of 18 to 29.9 kg/m^2. Participants were randomized to one of two treatment sequences (A-B, B-A). Treatment A was a

single oral dose of one 10 mg finerenone IR tablet in the fasted state. Treatment B was from Day -4 to Day -0,12H where 600 mg gemfibrozil was given BID in the fasted state, a single oral dose of 1 x 600 mg gemfibrozil tablet was given at Day -0,1H, followed 1 hour later at Day 0,0H by a single oral dose of 1 x 10 mg finerenone IR tablet in the fasted state, then at Day 0,9.5H, a single oral dose of 600 mg gemfibrozil was given in the fasted state. The main PK parameters were AUC and C_{max} of finerenone.

Results

Table 126. Point Estimators (LS-Means) and Exploratory Two-Sided 90% CIs and 95% Prediction Intervals for the Ratio of "10 mg Finerenone + Gemfibrozil/10 mg Finerenone" of AUC and C_{max} of Finerenone and Its Metabolites

Parameter	n	Geom. CV (%)	Estimated Ratio (%)	90% Confidence Interval (%)	95% Prediction Interval (%)
Finerenone					
AUC	16	17.9	110.05	[98.55 ; 122.89]	[63.23 ; 191.53]
C_{max}	16	31.4	115.67	[95.59 ; 139.98]	[44.39 ; 301.40]
M-1					
AUC	16	18.9	105.56	[93.93 ; 118.61]	[58.77 ; 189.59]
C_{max}	16	21.3	108.47	[95.16 ; 123.65]	[56.21 ; 209.32]
M-2					
AUC	16	12.3	106.42	[98.60 ; 114.86]	[72.54 ; 156.11]
C_{max}	16	12.1	108.63	[100.76 ; 117.11]	[74.46 ; 158.48]
M-3					
AUC	16	10.8	95.54	[89.33 ; 102.17]	[68.19 ; 133.85]
C_{max}	16	16.8	97.74	[88.08 ; 108.46]	[57.96 ; 164.82]

Source: Applicant, Study 15112, Report PH-38930, Table 2-1.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean

Reviewer's Comment

Overall, both total systemic exposures and C_{max} of finerenone and its metabolites were similar (Table 126). Consistent with in vitro findings, these results suggest that CYP2C8 is not the primary metabolic pathway and strong inhibitors of CYP2C8 do not affect the exposures to finerenone or its metabolites.

Interaction Study to Investigate the Influence of a Co-Administration of a Single Dose of 10 mL Maalox® and a 4-Day Pre- and Cotreatment With Omeprazole 40 mg OD, Respectively, on the Pharmacokinetics of a Single Dose of 10 mg Finerenone IR-Tablet in a Threefold Crossover, Randomized, Open-Label Design in Healthy Male Subjects (Study 14506)

Study Design

The primary objectives were to investigate the influence of a co-administration of a single dose of 10 mL Maalox 70 mVal suspension and a 4-day pre- and co-treatment of 40 mg omeprazole once daily (given as 2 x 20 mg Antra) on the PK of finerenone given as a single dose10 mg IR tablet in comparison to a single oral dose of 10 mg finerenone alone in a 3-way crossover,

randomized, open-label design. The participants were healthy male white subjects aged 18 to 46 years with a BMI of 18 to 22.9 kg/m^2. Primary PK parameters of finerenone were AUC and C_{max}. This was a 3-way crossover design. Treatment A was a single oral dose of 10 mg finerenone IR tablet in the fasted state. In treatment B, on Days -4 to -1, 40 mg omeprazole was given as 2 x 20 mg Antra, once daily in the ambulant setting, and on Day 0, 40 mg omeprazole was given as a single dose followed 2 hours later by 10 mg finerenone IR tablet in the fasted state. In treatment C, at day 0, a single oral dose of 10 mL Maalox 70 mVal suspension was given, followed immediately by a single oral dose of 10 mg finerenone IR tablet in the fasted state. There was a wash-out period of at least 96 hours after administration of the test substance after each period.

Results

Table 127. Point Estimates (LS-Means) and 2-Sided 90% CI for the Treatment Ratios of AUC and C_{max} of Finerenone

Ratio	Parameter	n	Estimated ratio (%)	90% confidence interval (%)
BAY 94-8862 10 mg + omeprazole 40 mg / BAY 94-8862 10 mg alone	AUC	11	104.52	[92.60 ; 117.96]
	C_{max}	11	98.81	[80.66 ; 121.04]
BAY 94-8862 10 mg+ Maalox 10 mL / BAY 94-8862 10 mg alone	AUC	10	102.20	[90.11 ; 115.91]
	C_{max}	10	81.16	[65.71 ; 100.24]

Source: Applicant, Study 14506 Report, Table 2-2.
Abbreviations: AUC, area under the curve; CI, confidence interval; LS-mean, least squares mean

Reviewer's Comment

Pre- and co-administration with omeprazole did not affect the rate and extent of finerenone absorption. Co-administration with Maalox 10 mL did not influence the extent of finerenone absorption; however, there was a small decrease in the rate of absorption (Table 127).

Single-Center, Randomized, Non-Blinded, Non-Placebo-Controlled, Two-Way Cross-Over Study to Investigate the Influence of Multiple Doses of 20 mg OD Finerenone on Pharmacokinetics, Safety and Tolerability of a Single Oral Dose of 7.5 mg Midazolam in Comparison to a Single Dose of 7.5 mg Midazolam Alone in Healthy Male Subjects (Study 15111)

Study Design

The primary objective was to assess the influence of multiple doses of 20 mg finerenone administered once daily for 10 days on the pharmacokinetics of a single oral dose of 7.5 mg midazolam. The secondary objective of the study was to assess the influence of multiple doses of 20 mg finerenone administered once daily for 10 days on the safety and tolerability of a single oral dose of midazolam. Participants were healthy male subjects aged 18 to 45 years with a BMI of 18 to 29.9 kg/m^2. Subjects were randomized to Treatment A (single dose of midazolam) followed by Treatment B (10 days of finerenone with a single dose of midazolam on the last day), or vice versa (Treatment B followed by Treatment A). There was to be a washout period of

at least 9 days between treatments. For assessment of PK, the primary variables were AUC and C_{max} of midazolam.

Results

Table 128. Point Estimates (LS-Means), 90% CIs, and 95% PIs for the Ratio 'Midazolam + Finerenone/Midazolam' for Selected PK Parameters

Parameter	n	Geo. CV (%)	LS-mean	90% CI	95% PI
Midazolam					
AUC	30	18.72	1.1056	[1.0190; 1.1995]	[0.6401; 1.9097]
C_{max}	30	46.90	1.0921	[0.8979; 1.3283]	[0.2938; 4.0594]
1´-hydroxymidazolam					
AUC	28	19.62	0.9962	[0.9118; 1.0885]	[0.5610; 1.7691]
C_{max}	30	56.20	0.9938	[0.7895; 1.2509]	[0.2124; 4.6490]
Metabolic ratio					
MR_{AUC}	28	17.47	0.9045	[0.8357; 0.9788]	[0.5419; 1.5096]
$MR_{AUC(0\text{-}tlast)}$	30	16.67	0.9122	[0.8482; 0.9810]	[0.5603; 1.4852]

Source: Applicant, Study 15111, Report PH-39782, Table 9-6.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PI, prediction interval; PK, pharmacokinetic

Reviewer's Comment

Total systemic exposure and C_{max} of midazolam remained largely unaffected with pre-treatment and co-administration of 20 mg finerenone with midazolam This implies finerenone is not an inhibitor of CYP3A4 in vivo (Table 128).

Randomized, Open-Label, Non-Placebo-Controlled, Three-Way Cross-Over Study to Investigate the Effect of a Single Dose of 20 mg Finerenone Given Concomitantly or 3 Hours Before Repaglinide on the Pharmacokinetics, Safety and Tolerability of a Single Oral Dose of 0.5 mg Repaglinide in Comparison to 0.5 mg Repaglinide Alone in Healthy Male Subjects (Study 16541)

Study Design

The primary objective of this study was to investigate the influence of a single oral dose of finerenone 20 mg on the pharmacokinetics of 0.5 mg repaglinide, given as a single oral dose in combination with 20 mg finerenone or 3 hours after administration of 20 mg finerenone, in comparison to 0.5 mg repaglinide given alone. The secondary objective of this study was to assess the effect of a single oral dose of finerenone 20 mg on the pharmacokinetics of 0.5 mg repaglinide, given as a single oral dose in combination with 20 mg finerenone or 3 hours after administration of 20 mg finerenone, in comparison to 0.5 mg repaglinide given alone. The participants were healthy white male subjects aged 18 to 45 years with a BMI of 18 to 29.9 kg/m^2. Treatment A was a single oral dose of 0.5 mg repaglinide in the fasted state (15 minutes before breakfast). Treatment B was a single oral dose of 20 mg finerenone concomitantly given with 0.5 mg repaglinide in the fasted state (15 minutes before breakfast). Treatment C was a single oral dose of 20 mg finerenone given in the fasted state followed 3 hours later by 0.5 mg repaglinide in the fasted state (15 minutes before breakfast).

Results

Table 129. Point Estimators (LS-Means), Two-Sided Explorative 90% CIs and 95% Prediction Intervals for Ratios of AUC and C_{max} of Repaglinide

Ratio	Parameter	Unit	n	Geom. %CV	Estimated Ratio (%)	90% CI (%)	95% PI (%)
B/A	AUC	ug*h/L	25	11.0	111.59	[105.92 ; 117.57]	[81.19 ; 153.39]
	C_{max}	ug/L	28	20.1	104.88	[95.57 ; 114.25]	[58.81 ; 185.64]
C/A	AUC	ug*h/L	24	11.0	110.19	[104.52 ; 116.17]	[80.16 ; 151.46]
	C_{max}	ug/L	28	20.1	106.69	[95.59 ; 114.28]	[58.83 ; 185.70]

Abbreviations: CI=confidence interval, LS=least squares; PI=prediction interval.
A = Repaglinide 0.5 mg
B = Repaglinide 0.5 mg and concomitant finerenone 20 mg
C = Repaglinide 0.5 mg administered 3 hours after finerenone 20 mg
Source: Applicant, Study 16541, Report PH-38625, Table 2-2.
Abbreviations: AUC, area under the curve

Table 130. PK Parameters of Finerenone in Plasma (Geometric Mean/CV% [Range])

Parameter	Unit	Repaglinide 0.5 mg and concomitant finerenone 20 mg (N=28)	Repaglinide 0.5 mg administered 3 hours after finerenone 20 mg (N=28)
AUC	ug*h/L	431/30.8 (248-828)	392/33.8 (164-693)
AUC(0-t_{last})	ug*h/L	430/30.9 (247-826)	391/33.8 (164-692)
C_{max}	ug/L	187/39.1 (70.5-333)	140/33.7 (88.0-247)
t_{max}[a]	h	0.733 (0.467-5.00)	0.967 (0.467-3.98)
$t_{½}$	h	2.32/22.4 (1.50-3.16)	2.22/28.0 (1.20-3.81)

a Data are presented as median (range)
Source: Applicant, Study 16541, Report PH-38625, Table 2-3.
Abbreviations: AUC, area under the curve; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Reviewer's Comment

20 mg finerenone had no effect on the exposure of repaglinide, a CY2C8 substrate. This indicates that finerenone is likely not a clinically relevant inhibitor of CYP2C8; however, repaglinide did increase the C_{max} and AUC of finerenone, although not as much as with concomitant administration of weak and moderate CYP3A4 inhibitors (Table 129).

No specific study was conducted to assess the effect of finerenone on OATP1B1/3; however, this study provides insight into this issue because repaglinide is also an OATP substrate. Because the change in C_{max} of repaglinide, although small, was similar when finerenone was co-administered and when administration was separated by 3 hours, the effect of finerenone on inhibition of OATP transport protein can be ruled out (Table 130). With regard to the effect of co-administration on blood glucose lowering, the mean maximum decrease in blood glucose was 30% higher when repaglinide and finerenone were co-administered than when repaglinide was administered alone; however, the %CV for the maximum decrease in blood glucose ranged from 55 to 132%. Given the high variability, it is challenging to draw definite conclusions from these data about whether co-administration results in a greater blood glucose lowering effect than administration of repaglinide alone.

Randomized, Double-Blind, Placebo-Controlled, 2-Way Cross-Over Study to Investigate the Effects of Finerenone, Administered as 20 mg IR Tablets Once-Daily Over 6 Days, on the Safety, Tolerability, Pharmacodynamics and Pharmacokinetics of Warfarin in Healthy Male Subjects (Study 14503)

Study Design

The primary objective of this study was to investigate if there was any PD or PK interaction when finerenone and warfarin were co-administered in healthy subjects, with respect to warfarin. The secondary objectives were the investigation of the pharmacokinetics of finerenone alone and after concomitant administration with warfarin, as well as the assessment of safety and tolerability of these treatments. 20 mg finerenone was administered once daily for 6 days. 3 doses of warfarin were given – a single priming dose of 25 mg warfarin at Day -21, 25 mg warfarin on Day 3 of finerenone treatment, and 25 mg warfarin on Day 3 of placebo treatment. Participants included healthy white male subjects 18 to 45 years old. The primary PD parameters were $AUC_{(0\text{-}96h)}$ of prothrombin time and of clotting factor VII, and the secondary parameters were $AUC_{(0\text{-}96h)}$ of clotting factors II and X.

Results

Table 131. Point Estimates, 90% CI, and 95% Prediction Intervals for the Ratio of Warfarin + Finerenone/Warfarin + Placebo of Primary and Secondary PD Parameters

Parameter	Unit	Geo.CV (%)	LS-mean	90% Confidence interval	95% Prediction interval
AUC(0-96h) PT	%·h	4.40	1.0136	[0.9905; 1.0372]	[0.8883; 1.1567]
AUC(0-96h) Factor VII activity	%·h	14.2	1.0416	[0.9683; 1.1204]	[0.6818; 1.5912]
AUC(0-96h) Factor II activity	%·h	3.21	1.0106	[0.9944; 1.0271]	[0.9178; 1.1129]
AUC(0-96h) Factor X activity	%·h	5.08	1.0097	[0.9829; 1.0371]	[0.8670; 1.1758]

Source: Applicant, Study 14503, Report PH-38718, Table 2-1.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PD, pharmacodynamic; PT, prothrombin time

Table 132. Point estimates, 90% CI, and 95% Prediction Intervals for the Ratio Warfarin + Finerenone / Warfarin + Placebo (for R- and S-Warfarin Parameters) and Finerenone + Warfarin / Finerenone (for Finerenone Parameters)

	Parameter	Unit	Geo.CV (%)	LS-mean	90% CI[a]	95% Prediction interval
R-warfarin	AUC	µg·h/L	6.0784	0.9925	[0.9627; 1.0233]	[0.8275; 1.1904]
	C_{max}	µg/L	7.3034	1.0355	[0.9983; 1.0742]	[0.8324; 1.2882]
S-warfarin	AUC	µg·h/L	5.5802	0.9953	[0.9678; 1.0236]	[0.8423; 1.1761]
	C_{max}	µg/L	7.1703	1.0294	[0.9930; 1.0672]	[0.8308; 1.2755]
Finerenone	$AUC_{T,md}$	µg·h/L	6.0638	0.9674	[0.9388; 0.9968]	[0.8073; 1.1592]
	$C_{max,md}$	µg/L	33.9777	0.9327	[0.7920; 1.0984]	[0.3476; 2.5024]

a Please note that 90% CIs are confirmatory for PK parameters of R- and S-warfarin and exploratory for PK parameters of finerenone

Source: Applicant, Study 14503, Report PH-38718, Table 2-2.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation; LS-mean, least squares mean; PK, pharmacokinetic

Reviewer's Comment

Secondary PD parameters indicate that finerenone has no effect on the activity of warfarin as assessed by effects on factor II and factor X activity. There was a minimal effect on factor VII activity. Overall exposure and peak plasma concentrations of warfarin were not changed significantly when administered with finerenone; and vice versa (Table 131 and Table 132).

Randomized, Non-Blind, Non-Placebo-Controlled, 2-Way Cross-Over Study With Additional 1st Period With Fixed Treatment to Investigate the Pharmacokinetic Interaction Between Finerenone (20 mg Once-Daily) and Digoxin (0.375 mg Once-Daily) and to Investigate the Safety and Tolerability of the Combined Administration in Healthy Male Subjects (Study 14505)

Study Design

The primary objective of this study was to investigate the influence of concomitant intake of multiple doses of 20 mg finerenone administered once daily for 10 days on the steady state PK of digoxin (0.375 mg once daily). The secondary objectives were to examine safety and tolerability of the combined administration of both drugs and to determine the influence of multiple doses of digoxin (0.375 mg once daily) on the PK of a single dose of 20 mg finerenone. Participants were healthy white male subjects who were 18 to 45 years with a BMI of 18 to 29.9 kg/m^2. Participants were randomized to one of 2 treatment sequences: A-B-C, or A-C-B. Treatment A was a single oral administration of 20 mg finerenone. Treatment B was administration of 0.375 mg digoxin OD from Day -4 to Day 10. Treatment C was administration of 0.375 mg digoxin OD from day -4 to Day 10 and administration of 20 mg finerenone on Day 1 to Day 10.

Results

Table 133. Point Estimates, 2-Sided 90% CI, and 95% Prediction Intervals for the Ratio "Digoxin + Finerenone / Digoxin Alone" of $AUC_{T,md}$ and C_{trough} of Digoxin.

Parameter	n	Geom. CV (%)	Estimated Ratio	90% Confidence Interval	95% Prediction Interval
$AUC_{T,md}$	24	13.0	1.0172	[0.9540 ; 1.0846]	[0.6905 ; 1.4984]
C_{trough} (Day 8)	24	13.0	1.0187	[0.9552 ; 1.0865]	[0.6905 ; 1.5029]
C_{trough} (Day 9)	24	19.2	1.1010	[1.0021 ; 1.2096]	[0.6238 ; 1.9431]
C_{trough} (Day 10)	24	17.7	0.9670	[0.8863 ; 1.0550]	[0.5713 ; 1.6366]

Source: Applicant, Study 14505, Report PH-39189, Table 2-3.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation

Table 134. Point Estimates, 2-Sided 90% CI, and 95% Prediction Intervals for the Ratio "Digoxin + Finerenone / Finerenone Alone" of $AUC_{T,md}$ and C_{trough} of Finerenone.

Parameter	n	Geom. CV (%)	Estimated Ratio	90% Confidence Interval	95% Prediction Interval
AUC	24	19.0	0.9959	[0.9073 ; 1.0930]	[0.5678 ; 1.7468]
C_{max}	24	35.2	0.9658	[0.8156 ; 1.1437]	[0.3482 ; 2.6789]

Source: Applicant, Study 14505, Report PH-39189, Table 2-4.
Abbreviations: AUC, area under the curve; CI, confidence interval; CV, coefficient of variation

Reviewer's Comment

20 mg finerenone given concomitantly with 0.375 mg digoxin did not affect the PK of digoxin at steady state (Table 133). This rules out finerenone's P-gp inhibition potential. Co-medication with digoxin at 0.375 mg had no effect on the single dose PK of finerenone (Table 134).

Bioequivalence Study Between Formulations (Study 20921, Report PH-41449)

Study Design

Clinical trials used 2 types of tablets (the so called "Phase I-IIa" and "Phase IIb-III formulations). The Applicant conducted retrospective and pooled analysis comparing finerenone AUC and C_{max} after dose normalization in clinical pharmacological studies. Clinical studies that used each formulation are presented in Table 135.

Table 135. Use of Finerenone Tablet Formulation Type in Clinical Pharmacological Studies

Finerenone tablet type	Strength [mg]	Studies using this formulation / strength
Phase I-IIa	1.25	14504, 15526, 15528,
	10	13784, 13785, 13786, 14502, 14506, 14508, 14509, 15526, 15528, 15171
Phase IIb-III	1.25	15481
	2.5	15481
	5	14503, 14510, 15481, 16535, 16541, 16910,
	7.5	15481
	10	15112, 15481, 16536, 16537, 18290
	20	14505, 15111, 15113, 16536, 16537, 16538, 19092

Source: Applicant, 2.7.1. Summary of Biopharmaceutics and Associated Analytical Methods, Table 3-1.

Results

The retrospective and pooled analysis comparing finerenone AUC and C_{max} after dose-normalization in clinical pharmacological studies demonstrated equivalent finerenone exposure, independent of the type of tablet given. Results are presented in Table 136.

Table 136. Assessment of Formulation Type-Ratio of Finerenone Exposure in Plasma (PK Analysis Set)

			90% confidence interval	
Parameter	Ratio	Estimate of ratio (LS-Mean)	Lower	Upper
AUC/D (h/L)	Tablet Phase I/IIa / Tablet Phase IIb/III	0.9093	0.8488	0.9740
CMAX/D (/L)	Tablet Phase I/IIa / Tablet Phase IIb/III	1.0336	0.9667	1.1052

Source: Applicant Report PH-41449, Table 14.4 / 20.
Abbreviations: AUC, area under the curve; LS-mean, least squares mean; PK, pharmacokinetic

Both core composition and [redacted] (b) (4) are identical between the clinical Phase IIb-III formulation and proposed commercial products whereas differences exist [redacted] (b) (4).

Reviewer's Comment

There was equivalent finerenone exposure, independent of the type of tablet applied. The 90% CIs were contained within the 80 to 125% bioequivalence range.

A Randomized, Double-Blind, Multi-Center Study to Assess Safety and Tolerability of Different Oral Doses of BAY 94-8862 in Subjects With Stable Chronic Heart Failure With Left Ventricular Systolic Dysfunction and Mild (Part A) or Moderate (Part B) Chronic Kidney Disease Versus Placebo (Part A) or Versus Placebo and Spironolactone (Part B) (Study 14563 – Phase IIa)

Study Design

The ARTS Study (mineralocorticoid-Receptor antagonist Tolerability Study) was a phase 2a safety study of different oral doses of finerenone in stable chronic heart failure subjects with left ventricular systolic dysfunction and mild (Part A) or moderate (Part B) CKD. The objective in Part A of the study was to investigate the safety and tolerability of 3 oral doses of finerenone given once daily over 4 weeks in a randomized, placebo-controlled, double-blind study design in subjects with chronic heart failure with left ventricular systolic dysfunction and mild CKD (60 mL/min/1.73 $m^2 \leq$ eGFR <90 mL/min/1.73 m^2). The primary objective of Part B was to investigate the change in serum potassium after treatment with 4 oral dosages of finerenone given once or twice daily over 4 weeks in a randomized, placebo-controlled, double- blind study design versus placebo and active comparator, spironolactone, in subjects with chronic heart failure with left ventricular systolic dysfunction and moderate CKD (30 mL/min/1.73 $m^2 \leq$ eGFR $\leq$60 mL/min/1.73 m^2). In addition to assessing effects on serum potassium, in both Parts A and B, the effects of these doses on changes in biomarkers of renal function [cystatin C, kidney injury molecule-1 (KIM-1), and neutrophil gelatinase-associated lipocalin (NGAL)], eGFR using the Modification of Diet in Renal Disease (MDRD) Study Group formula, albuminuria, and pharmacokinetics of finerenone and its metabolites in plasma after multiple oral doses were assessed. The study also assessed the PK of finerenone and its metabolites in plasma after

multiple oral doses. The doses in Part A were 2.5 mg, 5 mg, and 10 mg once daily. The doses in Part B were 2.5 mg, 5 mg, and 10 mg once daily, or 5 mg BID. In Parts A and B, there was a placebo reference. In Part B, there was also a spironolactone reference with a starting dose of 25 mg once daily and up-titration to 50 mg once daily after 2 weeks of treatment if serum potassium was ≤4.8 mmol/L.

Results

Table 137. Mean Change in Serum Potassium [mmol/L] From Baseline to the Average of Visit 6 (Day 22±2) and Visit 7 (Day 29±2) in Part B (ANCOVA Model, No Imputation Performed).

Treatment group	Adjusted mean	Standard error	95% confidence interval Lower limit	Upper limit
2.5 mg BAY 94-8862 OD	0.04	0.04	-0.04	0.13
5 mg BAY 94-8862 OD	0.16	0.04	0.07	0.24
10 mg BAY 94-8862 OD	0.21	0.04	0.13	0.29
5 mg BAY 94-8862 BID	0.30	0.04	0.21	0.38
Spironolactone	0.45	0.05	0.36	0.54
Placebo	0.08	0.04	-0.01	0.16

Source: Applicant, Study 14563, Report A52945, Table 2-2.
Abbreviations: ANCOVA, analysis of covariance; BID, twice daily; OD, once daily

For those in Part A receiving 2.5 mg, 5 mg, or 10 mg once daily finerenone treatment, mean KIM-1 values at visit 1 were 0.18, 0.17, and 0.2 µg/L, respectively. At visit 6, the mean change from baseline was 0.03, 0.028, and -0.015 µg/L, respectively, and at follow-up, the mean change from baseline was 0.003, 0.105, and -0.002 µg/L, respectively. For those in Part B receiving 2.5 mg, 5 mg, or 10 mg once daily finerenone treatment, 5 mg BID finerenone treatment, or spironolactone, mean KIM-1 values at visit 1 were 0.28, 0.16, 0.29, 0.2, and 0.17 µg/L, respectively. At visit 7, the mean change from baseline was -0.072, 0.031, 0.11, -0.030, and -0.004 µg/L, respectively, and at follow-up, the mean change from baseline was -0.095, 0.014, 0.068, 0.01, and -0.002 µg/L, respectively.

For those in Part A receiving 2.5 mg, 5 mg, or 10 mg once daily finerenone treatment, mean NGAL values at visit 1 were 57, 41, and 34.3 µg/L, respectively. At visit 6, the mean change from baseline was -6.3, 7.3, and 1.8 µg/L, respectively, and at follow-up, the mean change from baseline was -28, 15.7, and -10.3 µg/L, respectively. For those in Part B receiving 2.5 mg, 5 mg, or 10 mg once daily finerenone treatment, 5 mg BID finerenone treatment, or spironolactone, mean NGAL values at visit 1 were 56.5, 56.8, 60.9, 49.2, and 107.6 µg/L, respectively. At visit 7, the mean change from baseline was -12.1, 12.2, -10.3, 17.8, and -23.2, respectively, and at follow-up, the mean change from baseline was 1.8, 7.6, 10.6, 12.5, and -21.3 µg/L, respectively.

Reviewer's Comment

In Part B, the 10 mg finerenone once daily group and the 5 mg BID group demonstrated a significantly higher increase in serum potassium than the placebo group. The 2.5 mg, 5 mg, and 10 mg once daily, as well as the 5 mg BID group had a significantly smaller increase in serum potassium than the spironolactone group (Table 137). All investigated doses of finerenone showed reductions in albuminuria, BNP, and NT-proBNP levels, with the exception of the 2.5 mg finerenone once daily group. There were no obvious changes in KIM-1 or NGAL levels during treatment or evidence of dose-dependent effects.

A Randomized, Double-Blind, Placebo-Controlled, Multi-Center Study to Assess the Safety and Efficacy of Different Oral Doses of BAY 94-8862 in subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Nephropathy (Study 16243)

Study Design

The ARTS-DN study was a phase 2b study to assess the safety and efficacy of finerenone in patients with type 2 diabetes mellitus and a clinical diagnosis of diabetic nephropathy. The primary objective was to investigate the change in urinary albumin-to-creatinine ratio (UACR) after treatment with different oral doses of finerenone given once daily (OD) from baseline to Visit 5 (Day 90±2). Background treatment included standard of care for renal and cardiovascular disease protection. Those included in the study were male and female subjects (≥18 years of age) with type 2 diabetes mellitus and a clinical diagnosis of DN treated with an ACEI and/or ARB for at least 3 months; subjects with an eGFR of 30 to 45 mL/min/1.73 m^2 (CKD-EPI) must also be treated with a non-potassium sparing diuretic at screening. The clinical diagnosis of DN was based on at least one of the following criteria: 1) persistent very high albuminuria defined as UACR of ≥300 mg/g (≥34 mg/mmol) in 2 out of 3 first morning void samples and estimated glomerular filtration rate (eGFR ≥30 mL/min/1.73 m^2 but <90 mL/min/1.73 m^2 (CKD-EPI), or 2) persistent high albuminuria defined as UACR of ≥30 mg/g but <300 mg/g (≥3.4 mg/mmol but <34 mg/mmol) in 2 out of 3 first morning void samples and eGFR ≥30 mL/min/1.73 m^2 but <90 mL/min/1.73 m^2 (CKD-EPI). Serum potassium had to be ≤4.8 mmol/L at screening. Participants were required to have a mean sitting systolic blood pressure (SBP) <180 mm Hg and mean sitting diastolic blood pressure (DBP) <110 mm Hg at the run-in visit and mean sitting SBP <160 mm Hg or mean sitting DBP <100 mm Hg at the screening visit.

Following an open-label run-in and screening period of up to 12 weeks, eligible subjects were randomized to one of 7 doses of finerenone or placebo on top of standard of care to receive a 90-day study drug treatment. Initially, the following 5 doses of finerenone and placebo were administered in a double-blind manner: 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, and 10 mg OD. After the safety and tolerability of these doses had been assessed by an independent DMC, 2 further doses of finerenone—15 mg and 20 mg OD—were introduced. AEs, including hyperkalemia, and pharmacokinetics were evaluated. UACR was also evaluated as a marker for efficacy.

Reviewer's Comment

*The primary efficacy analysis demonstrated a dose-dependent reduction in the ratio of UACR at Visit 5 (Day 90±2) to UACR at baseline. Statistically significant differences compared to placebo were observed for the doses of 7.5 mg, 10 mg, 15 mg, and 20 mg administered once daily, with the largest effects seen at the highest doses. The placebo-corrected reduction in UACR was 21, 25, 33, and 38% in the finerenone 7.5 mg OD, 10 mg OD, 15 mg OD, and 20 mg OD groups, respectively. Twelve of 821 subjects (1.5%), all in the finerenone treatment groups, experienced an AE of special interest, defined as an increase in potassium ≥5.6 mmol/L and subsequent discontinuation of study drug. All events of "hyperkalemia" and "blood potassium increased" resolved. For more on exposure-versus-serum potassium response, see Section 14.3.2.*informatio

14.3. Pharmacometrics Review

14.3.1. Population PK Analysis

14.3.1.1. Review Summary

The Applicant's population PK (PopPK) analysis was not acceptable for identifying covariates of finerenone clearance. This is because the Applicant's final PopPK model included correlated variables (eGFR-EPI versus creatinine and body weight versus race) as covariates on clearance and volume thus affecting the accuracy and precision of parameter estimates.

As one of the goals of the review was to evaluate additional covariates of finerenone clearance, the FDA reviewer developed an alternative PopPK model which avoided including correlated covariates. Evaluation of the models indicated that the FDA's PopPK model and Applicant's final model provide a comparable description of the PK data. The individual PK estimates from the FDA reviewer's final PopPK model were subsequently used for exposure-response analyses to support the proposed dosage of finerenone.

Both the Applicant and the FDA reviewer's final population PK model were 2 compartment models parameterized in clearance (CL/F), volume of the central compartment (Vc/F), volume of the peripheral compartment (Vp/F), transfer clearance between Vc and Vp (Q), and absorption through 3 transit compartments with first order absorption constant (Ka) and absorption lag time fixed to 0.215 hours. Population average for relative bioavailability (RF) was fixed to 1 and between subject variability (BSV) for RF was estimated in the FDA reviewer's PopPK model.

For the Applicant's model, the identified sources of variability for CL/F were the time varying eGFR-EPI, body height, creatinine, smoking status, gamma glutamyl transferase (GGT), and use of SGLT-2 inhibitors. The model also included the same variables (eGFR-EPI, body height, creatinine, smoking status, GGT, and SGLT-2 inhibitors) as covariates on relative bioavailability (F). Sources of Vc/F variability were body weight, and race/ethnicity (Korean subjects versus the rest). However, none of the covariates had significant impact on finerenone C_{max} and AUC, except race/ethnicity. Simulations indicated that Korean subjects would have 21.2% lower C_{max} as compared to subjects of other races/ethnicities.

In contrast, the FDA reviewer's final model identified time varying eGFR-EPI, body weight, and strong CYP3A4 inhibitors as covariates on CL/F. Sources of variability for F1 were smoking status and SGLT-2 inhibitors while body weight was the only covariate for Vc.

For the Applicant's PopPK model, the unexplained BSV was 31.2% for CL and 32.6% for both Vc and Vp. BSV was not estimated for RF. Using the FDA reviewer's model, BSV for CL and RF were 15.0% and 33.1% respectively. Variance for Vc was estimated to be negatively correlated to variance for CL with a correlation coefficient of -1.36, therefore BSV for Vc was calculated to be 17.5%.

For the Applicant's PopPK model, ETA Shrinkages for CL and Vc were 7% and 19%, respectively; for the FDA reviewer's model shrinkages for CL and RF were 35% and 10%, respectively. The estimated PK parameters appear reasonable.

The developed model was used to support labelling of finerenone in the current submission as outlined in Table 138.

Table 138. Reviewer's Specific Comments on Population PK Model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Finerenone dosing is based on renal function status and blood potassium levels.	A statistically and clinically meaningful exposure-efficacy relationship for time to progression of CKD or major cardiovascular event was identified, thus providing evidence of effectiveness.
	Extrinsic factor	During treatment, the dose may be increased, decreased or treatment stopped based on blood potassium levels.	A relationship between exposure and blood potassium elevation was identified, supporting the proposed potassium monitoring and dose adjustment strategy.
Derive exposure metrics for exposure-response analyses	Predicted individual PK parameters were used in exposure-efficacy/safety analyses.		The use of predicted individual PK parameters in E-R analyses is acceptable since the model performance was reasonable as indicated by GOF and PcVPC.
Predict exposures at alternative dosing regimen			The model was not used to assess predicted exposures at other doses.

Abbreviations: CKD, chronic kidney disease; E-R, exposure-response; GOF, goodness of fit; PcVPC, prediction-corrected visual predictive checks; PK, pharmacokinetic

14.3.1.2. Introduction

The primary objectives of this analysis were to:

- Develop a population pharmacokinetic model of finerenone.
- Identify sources of PK variability that may impact finerenone exposure.
- Generate predicted individual PK parameters for subsequent exposure-response analyses.

14.3.1.3. Applicant's PopPK Model development

Data

The analyses were based on PK data from one Phase 3 study. The study design, study population, and timing of blood samples collection are presented in Table 139.

The final NONMEM data file for analysis contained 5458 PK observations from 2284 subjects. Table 140 provide summary statistics of the baseline demographic and laboratory characteristics in the analysis dataset.

Table 139. Summary of Studies With PK Sampling Included in Population PK Analysis

Study	Dosage	PK Sampling
Study 16244, FIDELIO-DKD	10 mg OD tablet (starting dose for patients with eGFR between 25 and <60 mL/min/1.73m2), 20 mg tablet OD (Starting dose for patients with eGFR ≥60 mL/min/1.73m2). Dose could be up-titrated from 10 mg to 20 mg if blood potassium was ≤4.8 mmol/L and eGFR-EPI decrease was ≤30% below last measured value. Down-titration or interruption of study drug was permitted for safety reasons.	Sparse PK samples collected at trough on visit 3 (month 4) or visit 4 (month 8) after starting treatment. Sparse samples were also collected at yearly visits, one sample any time after last dose taken at home.

source: Reviewer's summary of data from Applicant's POP PK report (study_18523_report_13179, pages 30-32)
Abbreviations: eGFR, estimated glomerular filtration rate; OD, once daily; PK, pharmacokinetic

Table 140. Summary of Baseline Demographic and Laboratory Characteristics

Characteristic	Starting Dose	
	10 mg N=2112	20 mg N=172
Measurement (mean (SD))		
Age (years)	65.78 (8.83)	63.79 (8.13)
Weight (kg)	86.40 (19.74)	87.59 (18.29)
Height (cm)	166.50 (9.50)	167.79 (9.66)
BMI (kg/m^2)	31.02 (5.96)	31.02 (5.27)
BSA (m^2)	1.94 (0.24)	1.97 (0.23)
ALT (U/L)	20.67 (12.07)	24.38 (12.76)
AST (U/L)	20.64 (9.51)	22.70 (9.72)
Albumin (g/dL)	4.11 (0.33)	4.16 (0.34)
Bilirubin (mg/dL)	0.42 (0.21)	0.46 (0.27)
GGT (U/L)	38.32 (52.28)	40.91 (42.04)
ALP (U/L)	80.72 (30.03)	78.23 (28.29)
Serum Creatinine (mg/dL)	1.60 (0.39)	1.12 (0.21)
Serum Protein (g/dL)	7.00 (0.53)	6.98 (0.51)
eGFR-MDRD (mL/min/1.73 m^2)	41.95 (10.35)	62.61 (8.86)
eGFR-EPI (mL/min/1.73 m^2)	42.92 (11.02)	65.49 (9.44)
Age group (n (%))		
>=75 years	342 (16.2)	9 (5.2)
18 - 44 years	29 (1.4)	5 (2.9)
45 - 64 years	842 (39.9)	78 (45.3)
65 - 74 years	899 (42.6)	80 (46.5)
Sex (n (%))		
Female	641 (30.4)	46 (26.7)
Male	1471 (69.6)	126 (73.3)
Alcohol use (n (%))		
Abstinent	1265 (59.9)	101 (58.7)
Heavy	9 (0.4)	1 (0.6)
Light	718 (34.0)	62 (36.0)
Moderate	120 (5.7)	8 (4.7)
Smoking status (n (%))		
Current	311 (14.7)	31 (18.0)
Former	809 (38.3)	57 (33.1)
Never	992 (47.0)	84 (48.8)

Characteristic	Starting Dose	
	10 mg N=2112	20 mg N=172
Race (n (%))		
American Indian	48 (2.3)	8 (4.7)
Asian Indian	20 (0.9)	0 (0.0)
Black/African American	95 (4.5)	8 (4.7)
Chinese	243 (11.5)	18 10.5)
Japanese	180 (8.5)	11 (6.4)
Korean	53 (2.5)	2 (1.2)
Native Hawaiian	5 (0.2)	2 (1.2)
Not reported or multiple	81 (3.8)	9 (5.2)
Thailander or Others	100 (4.7)	2 (1.2)
White	1287 (60.9)	112 (65.1)
eGRF category (n (%))		
eGFR >=60	0 (0.0)	172 (100.0)
eGFR 25-<45	1232 (58.3)	0 (0.0)
eGFR 45-<60	880 (41.7)	0 (0.0)
Child Pugh Score (n (%))		
Certainly B	2 (0.1)	0 (0.0)
Likely A	2004 (94.9)	166 (96.5)
Likely B	106 (5.0)	6 (3.5)
Renal impairment (n (%))		
Mild	129 (6.1)	123 (71.5)
Moderate	1718 (81.3)	48 (27.9)
Normal	3 (0.1)	0 (0.0)
Severe	262 (12.4)	1 (0.6)
SGLT-2 inhibitors use (n (%))		
>50%	99 (4.7)	21 (12.2)
0-50%	107 (5.1)	12 (7.0)
None	1906 (90.2)	139 (80.8)
GLP-1 agonists use (n (%))		
>50%	180 (8.5)	17 (9.9)
0-50%	121 (5.7)	8 (4.7)
None	1811 (85.7)	147 (85.5)
CYP3A4 inhibitor use (n (%))		
Moderate Cyp inh <50%	65 (3.1)	10 (5.8)
Moderate Cyp inh >50%	39 (1.8)	7 (4.1)
None	508 (24.1)	48 (27.9)
Strong Cyp inh <50%	47 (2.2)	1 (0.6)
Strong Cyp inh >50%	17 (0.8)	1 (0.6)
Unclassified Cyp inh <50%	29 (1.4)	2 (1.2)
Unclassified Cyp inh >50%	34 (1.6)	1 (0.6)
Weak Cyp inh <50%	184 (8.7)	11 (6.4)
Weak Cyp inh >50%	1189 (56.3)	91 (52.9)
CYP3A4 inducer use (n (%))		
Moderate Cyp ind <50%	101 (4.8)	11 (6.4)
Moderate Cyp ind >50%	7 (0.3)	0 (0.0)
None	1685 (79.8)	141 (82.0)
Strong Cyp ind <50%	24 (1.1)	1 (0.6)
Strong Cyp ind >50%	1 (0.0)	1 (0.6)
Unclassified Cyp ind <50%	88 (4.2)	6 (3.5)
Unclassified Cyp ind >50%	14 (0.7)	0 (0.0)
Weak Cyp ind <50%	103 (4.9)	4 (2.3)
Weak Cyp ind >50%	89 (4.2)	8 (4.7)

Characteristic	Starting Dose	
	10 mg N=2112	20 mg N=172
CYP3A4 inhibitor at baseline (n (%))		
Moderate	46 (2.2)	8 (4.7)
None or unclassified	690 (32.7)	64 (37.2)
Strong	20 (0.9)	0 (0.0)
Weak	1356 (64.2)	100 (58.1)

Source: Reviewer's analysis
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; GGT, gamma-glutamyl transferase; GLP, glucagon-like peptide; MDRD, Modification of Diet in Renal Disease; SGLT, sodium-glucose linked transporter

Base Model

The Applicant's base model was adopted from an existing final PopPK model developed using PK data from Phase 2b studies in patients with T2D and diabetic nephropathy. Therefore, the base model was a two-compartment model in which Vc/F and Vp/F could not be identified separately and were kept equal. The delay in absorption was described by first order absorption through 3 transit compartments with an additional lag time of 0.215 hours. Baseline body weight (BW0) and eGFR-MDRD (EGFRMDRD0) were covariates on both CL/F and F. BSV were identified for absorption rate constant (KA), CL/F, and Vc/F. Furthermore, correlation between BSV-CL and BSV-Vc was identified. Residual error was described by a proportional error model.

Covariate Analysis

The first step in the Applicant's covariate analysis was to investigate covariate distributions and correlations among the covariates. The second step was to perform graphical exploration of ETA-vs- covariate plots. Two sets of covariates were tested for inclusion into the model. The first set of covariates was identified through graphical exploration of ETA-vs- covariate plots. The second set was pre-defined before the analysis and were tested regardless of results from graphical analysis; these included age, body weight, Child-Pugh Score, CYP3A4 inhibitor or inducer use, baseline and time-varying eGFR-MDRD or eGFR-EPI, ethnic groups, and chronic use of SGLT inhibitors. In addition to these sets of covariates, time-dependent changes in clearance was also investigated. Continuous covariates were evaluated using a power function and categorical covariates were parameterized as a fractional change.

After identification of potential covariates, the covariate model was built through the following steps:

- Univariate analysis: At this step all covariates were added individually into the base model. Only covariates that led to >3.84 decrease on model objective function were taken for the next step of covariate analysis.
- Forward inclusion: At this step, a covariate with largest $-\Delta OFV$ during the univariate analysis was retained in the model and other covariates were added sequentially. Only covariates with $\Delta OFV > -6.63$ were retained in the model.
- Backward deletion: All covariates added during the forward step were removed sequentially starting with the covariate that was included last. Only covariates which led to $\Delta OFV > 10.8$ were retained in the model.

- After backward elimination step, the BSV parameters, covariance terms and residual error model were re-evaluated.

Final Model

The stepwise covariate model building included the following relationships in the final model:

- Time-varying eGFR-EPI, body height, baseline creatinine, chronic use of SGLT inhibitors, and smoking as covariates on CL/F and F. In addition, baseline GGT was a covariate on CL/F alone;
- Body weight and race (Korean subjects versus others) were the only covariates on Vc/F;
- No covariates were identified for Ka.
- The parameter estimates for the final covariate model are listed in Table 141. The goodness-of-fit plots for the final covariate model are shown in Figure 25. The Prediction corrected Visual Predictive Check (PcVPC) plot for the final covariate model is shown in Figure 26. The impact of the identified covariates on finerenone $C_{max,md}$ and $AUC_{\tau,md}$ is illustrated in Figure 27.

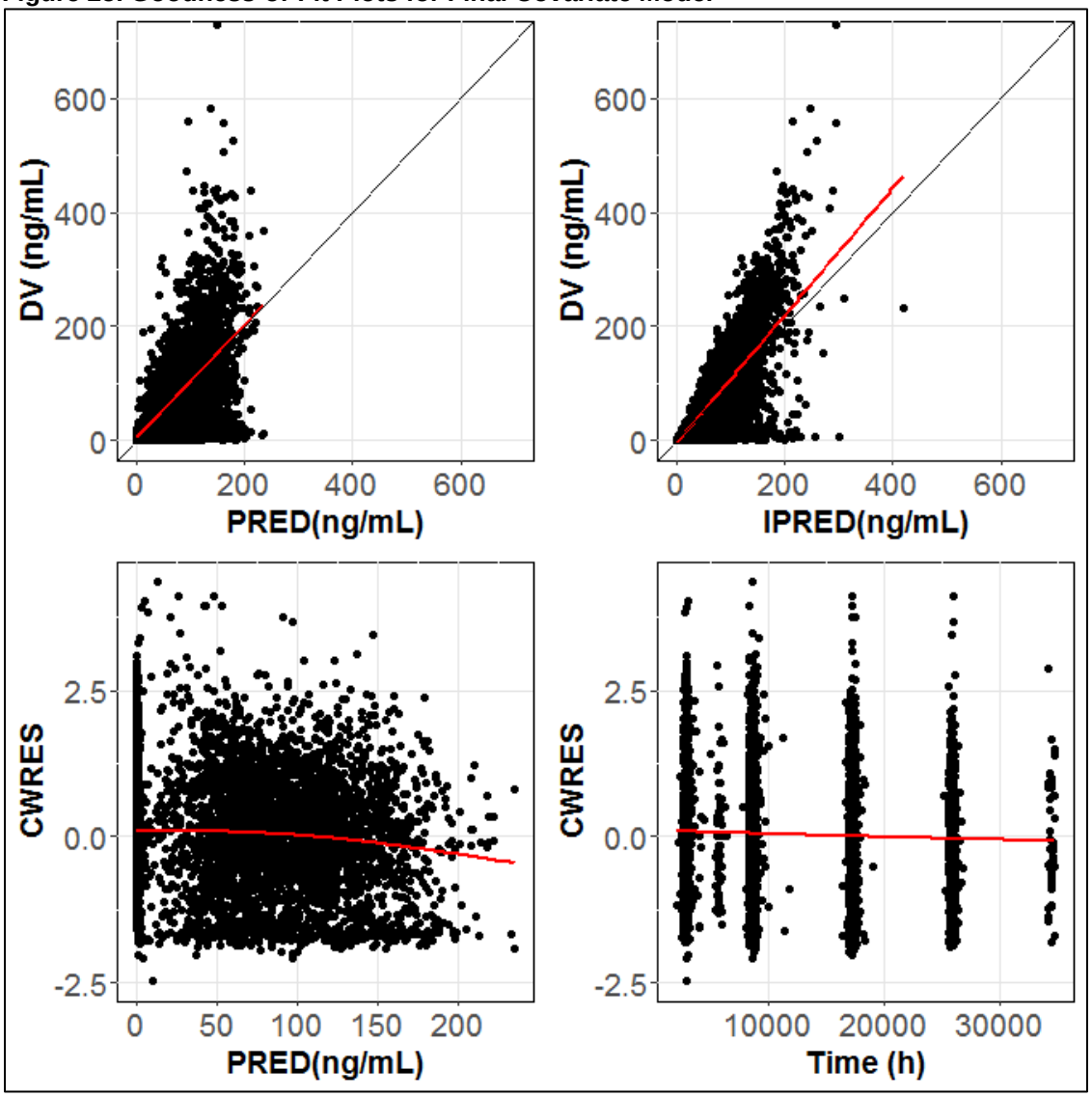
Table 141. Parameter Estimates From the Applicant's Final Population PK Model

Parameter Name	Estimate	SE	RSE (%)	95% CI
Ka (1/h)	22.4	3.15	14.1	(16.2, 28.6)
CL/F (L/h)	28.0	0.584	2.08	(26.9, 29.2)
Vc/F (L)	110	2.55	2.33	(105, 115)
Q/F (L/h)	0.325	0.0185	5.68	(0.289, 0.361)
Ratio between Vp/F and Vc/F (fixed)	1.00	-	-	(NA, NA)
Absorption lagtime (h) (fixed)	0.215	-	-	(NA, NA)
Relative bioavailability (fixed)	1.00	-	-	(NA, NA)
effect of WGHT0 on Vc/F	0.497	0.0498	10.0	(0.399, 0.594)
effect of EGFREP on CL/F and F	0.159	0.0250	15.7	(0.110, 0.208)
effect of HGHT0 on CL/F and F	0.712	0.117	16.4	(0.484, 0.941)
effect of CREA0 on CL/F and F	0.119	0.0330	27.7	(0.0543, 0.184)
effect of RACA (Korean subjects) on Vc/F	1.29	0.0883	6.83	(1.12, 1.47)
effect of SGLT (chronic SGLT-2 inhibitor use) on CL/F and F	1.10	0.0241	2.20	(1.05, 1.14)
effect of SMOK (current or former smokers) on CL/F and F	1.04	0.0116	1.11	(1.02, 1.06)
effect of GGT0 on CL/F	-0.0717	0.0108	-15.1	(-0.0928, -0.0505)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
CL/F	0.0979	0.00705	7.21	32.1
Vc/F and Vp/F	0.106	0.0201	18.9	33.5
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
residual error	0.313	0.00966	3.09	0.560

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(OM)-1)*100 in case of exponential variability or sqrt(OM)/TH*100 in case of additive variability, or presents the correlation coefficient (OMx,y / (sqrt(exp(OMx)-1) * sqrt(exp(OMy)-1))) for the covariance between parameters; StDev is calculated as sqrt(SIG), if SIG is defined already as StDev it will be the same as estimate

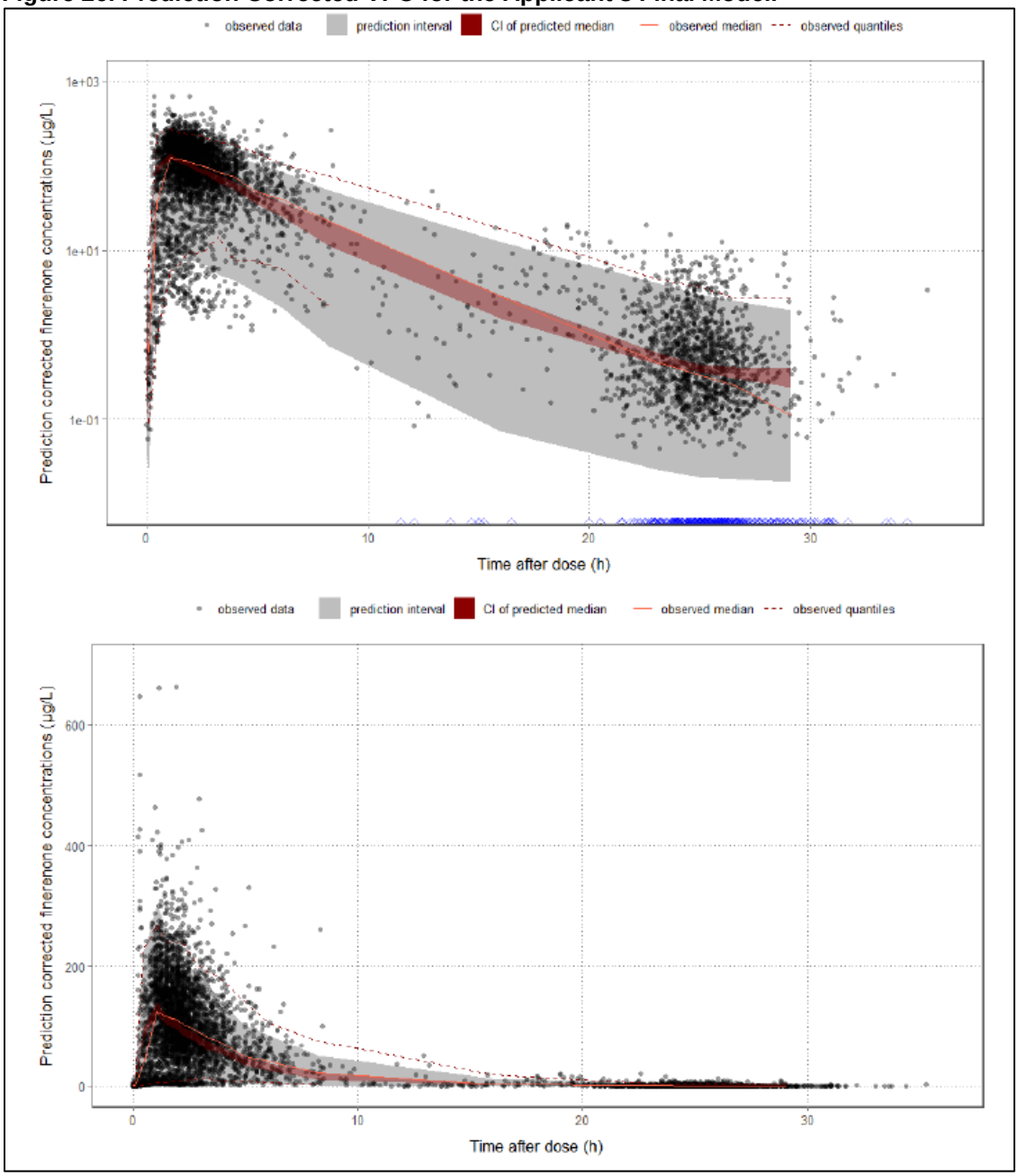
Source: Applicant's POP PK report (study_18523_report_13179, pages 52)
Abbreviations: CI, confidence interval; CL, clearance; CREA, creatinine; CV, coefficient of variation; PK, pharmacokinetic; RSE, relative standard error; SE, standard error; SGLT, sodium-glucose linked transporter

Figure 25. Goodness-of-Fit Plots for Final Covariate Model



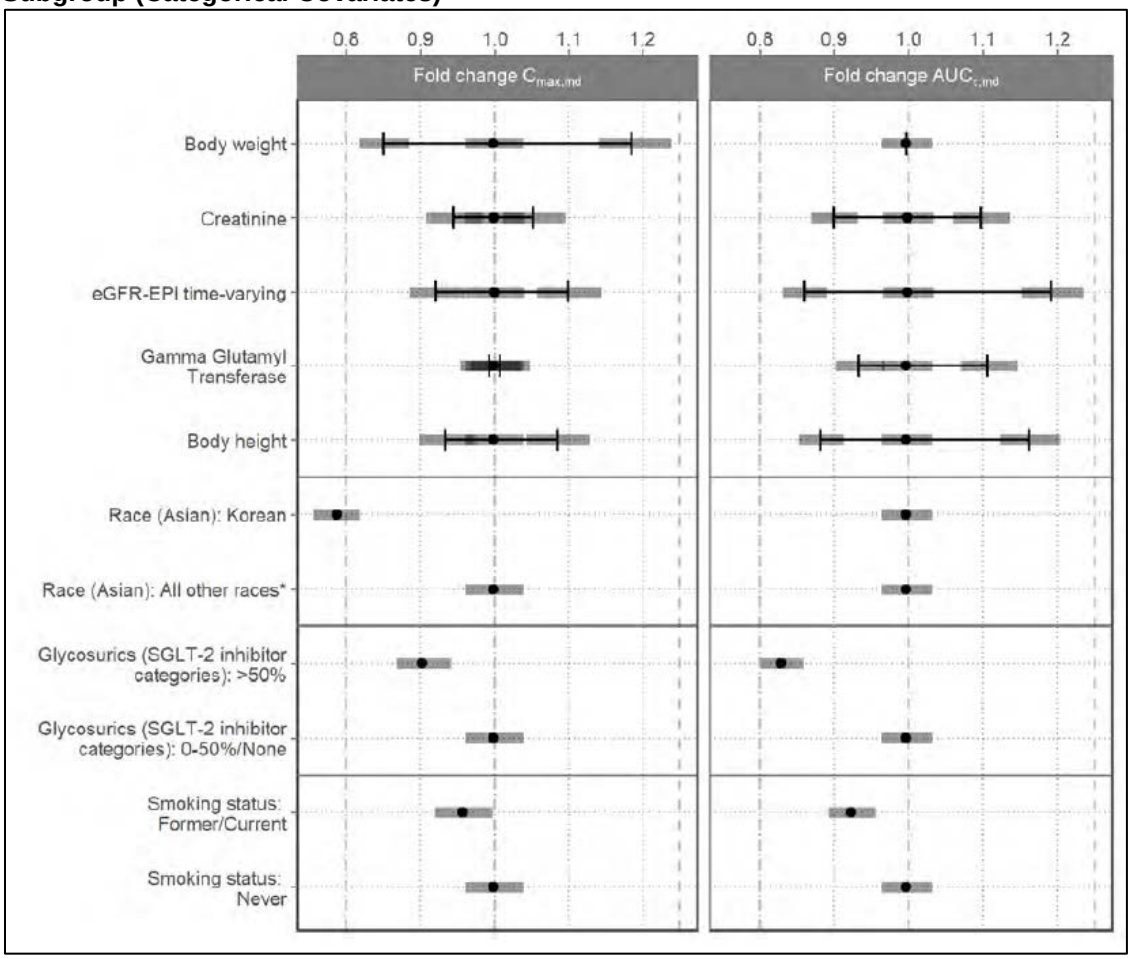
Source: Reviewer's post-processing of NONMEM outputs of the Applicant's pop PK model
Abbreviations: CWRES, weighted population residuals; DV, observations; PRED, predicted

Figure 26. Prediction Corrected VPC for the Applicant's Final Model.



Source: Applicant's POP PK report (study_18523_report_13179, pages 51)
Gray shared area represents 95% prediction interval, red solid band represent 95% variability-based prediction interval of the simulated medians (excluding parameter uncertainty), red line = observed median, red dashed lines =2.5th and 97.5th percentiles of observations.
Abbreviations: CI, confidence interval; VPC, visual predictive check

Figure 27. Forest Plots Illustrating the Influence of the Identified Covariate Effects on $C_{max,md}$ and $AUC_{0\text{-}Tau,md}$ Relative to the Median Covariate Value (Continuous Covariates) or Reference Subgroup (Categorical Covariates)

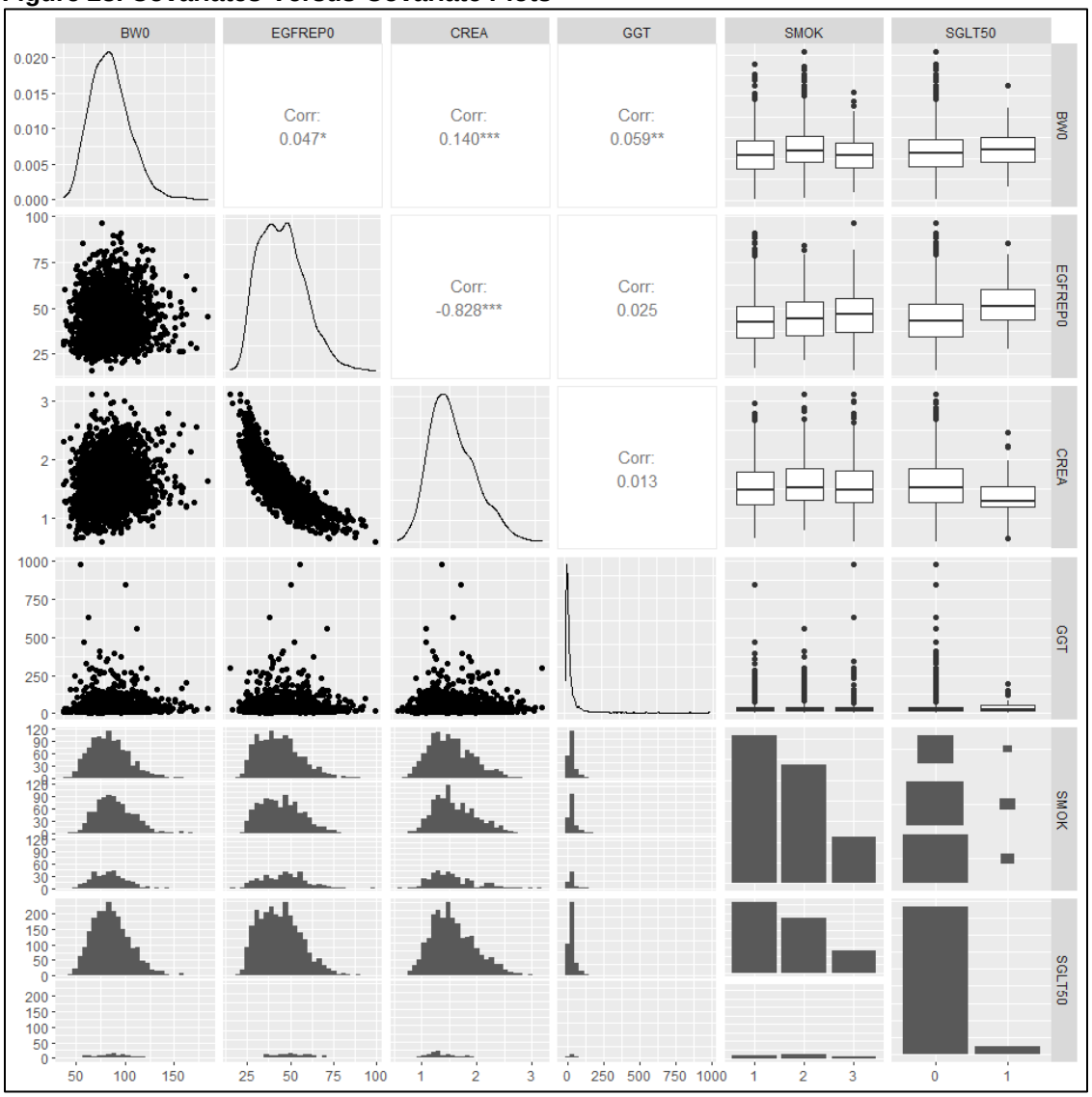


Source: Applicant's POP PK report (study_18523_report_13179, pages 53)
Abbreviations: AUC, area under the curve; eGFR, estimated glomerular filtration rate; SGLT, sodium-glucose linked transporter

Reviewer's Comment

The Applicant's final covariate model included several correlated covariates as shown in Figure 28. Correlated covariates were serum creatinine (CREA) and eGFR-EPI (EGFREP0). Similarly, SGLT inhibitor (SGLT50) use seems to be correlated with both serum creatinine and eGFR-EPI. Correlated covariates in a mixed effect model may impact estimation and precision of parameter estimates. Due to collinearity, covariate coefficients do not reflect the true inherent effect of a covariate. For this reason, the reviewer finds the Applicant's final model unacceptable for assessing the impact of the included covariates on finerenone exposure. The reviewer repeated covariate model development starting with the Applicant's base model. The reviewer's evaluation of model covariates and development of the final model are described in the section below.

Figure 28. Covariates-Versus-Covariate Plots



Source: Reviewer's analysis
Abbreviations: BW, body weight; CREA, creatinine; GGT, gamma-glutamyl transferase; SGLT, sodium-glucose linked transporter

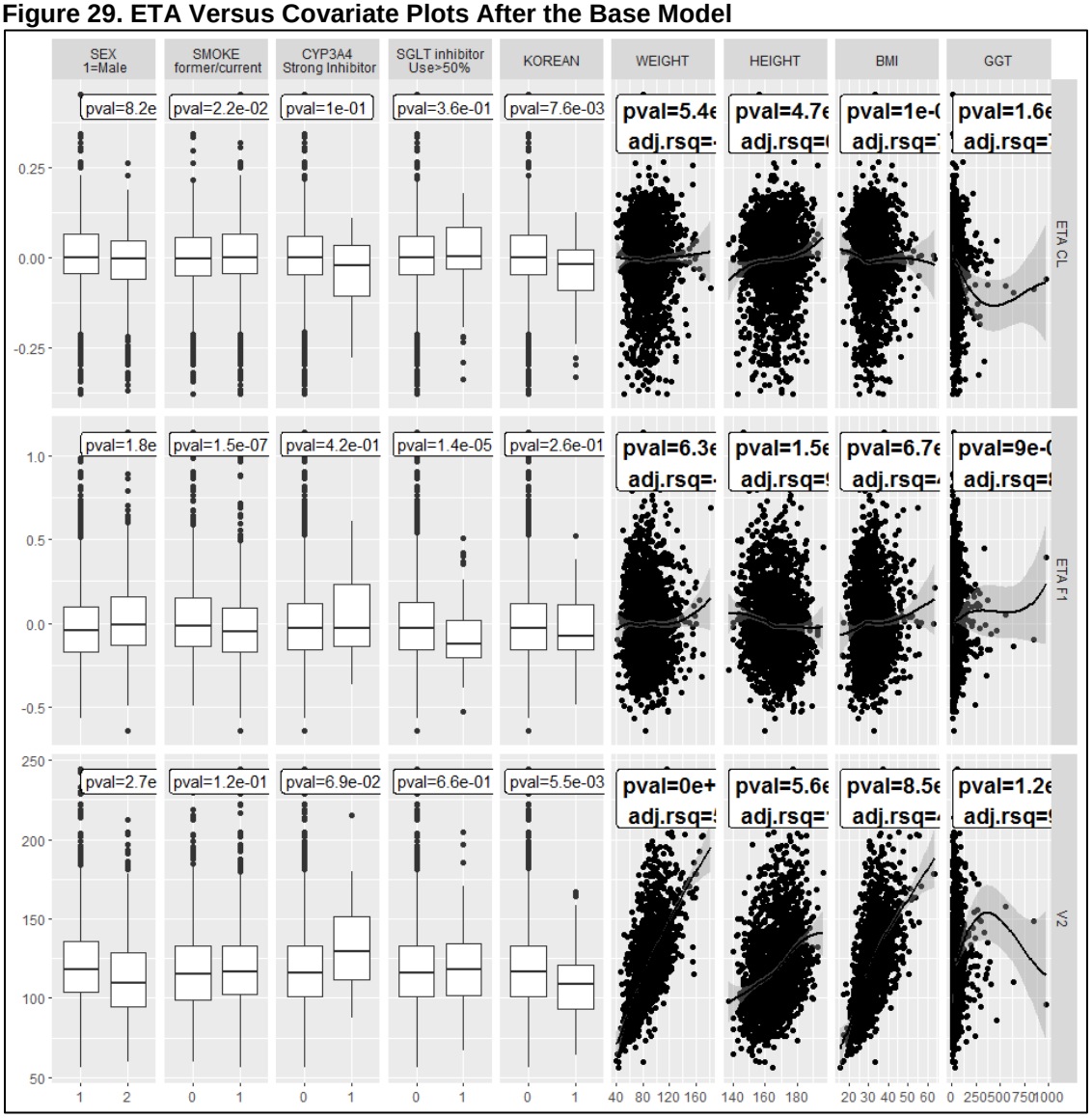
14.3.1.4. Reviewer's PopPK Model Development

The FDA reviewer used the same data and base structural model as described in Section 14.3.1.3. The base model was further optimized as follows:

- Body weight was included as a covariate on both CL/F and Vc/F using a power model and estimation of the exponents.
- BSV for bioavailability parameter F1 was estimated.
- Due to high covariance between BSV Vc/F and BSV CL/F, BSV of Vc/F was re-parameterized as scaled function of BSV of CL ($BSV\ Vc\ = \theta \times BSV\ CL$).
- For covariate model development ALAG1, Q and Vp were fixed to their last estimated values. This was necessary for NONMEM COVARIANCE step to generate plausible standard errors.

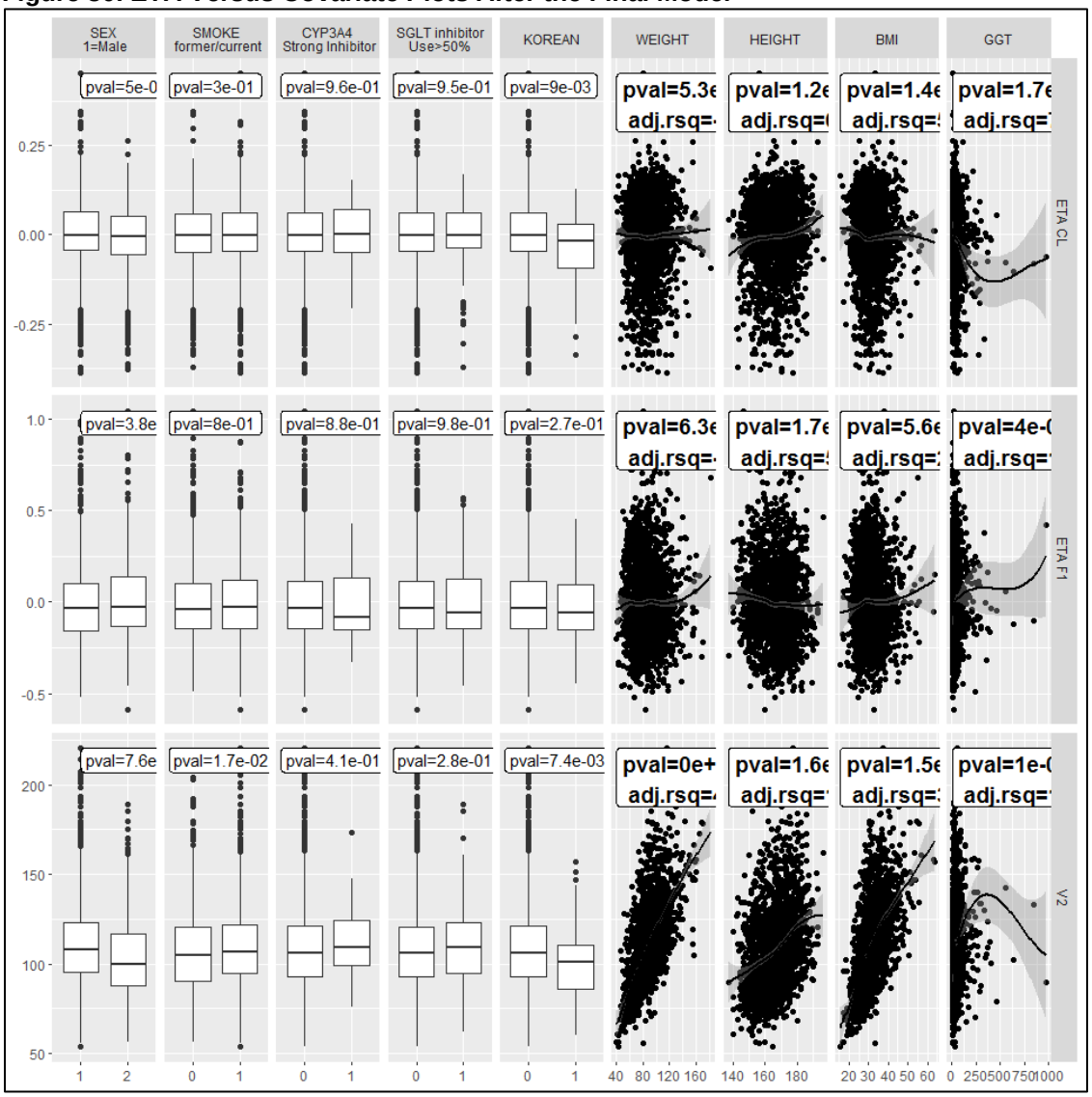
Graphical exploration of covariates versus ETA plots, and statistical comparisons of means or correlation analyses were used to identify potential covariates for inclusion into the model. The identified covariates were evaluated for biological plausibility. Only plausible parameter-covariate relations were added sequentially to the model. An included parameter-covariate relation was retained in the model if model OFV decreased by more than 3.84. After each covariate inclusion, graphical exploration of ETA versus covariate plots was used to re-assess the covariates for sequential addition into the model. The final model was achieved when no additional covariate was identified through both graphical-exploration/biological-plausibility and likelihood ratio test ($-\Delta OFV$>3.84). Figure 29 and Figure 30 show the plots of ETA versus covariates for included covariates for the base model and the final model, respectively.

Figure 29. ETA Versus Covariate Plots After the Base Model



Source: Reviewer's analysis
Abbreviations: BMI, body mass index; CL, clearance; CYP, cytochrome P450; GGT, gamma-glutamyl transferase; SGLT, sodium-glucose linked transporter

Figure 30. ETA Versus Covariate Plots After the Final Model



Source: Reviewer's analysis
Abbreviations: BMI, body mass index; CL, clearance; CYP, cytochrome P450; GGT, gamma-glutamyl transferase; SGLT, sodium-glucose linked transporter

Parameter estimates of the reviewer's final model are shown in Table 142. The parameters were well estimated (Standard errors <50%). Only time-varying eGFR-EPI, body weight, and use of strong CYP3A4 inhibitors were significant covariates on CL/F. Similarly, only chronic use of SGLT inhibitors and cigarette smoking (current or former) were significant covariates on F1. Body weight was the only covariate on Vc.

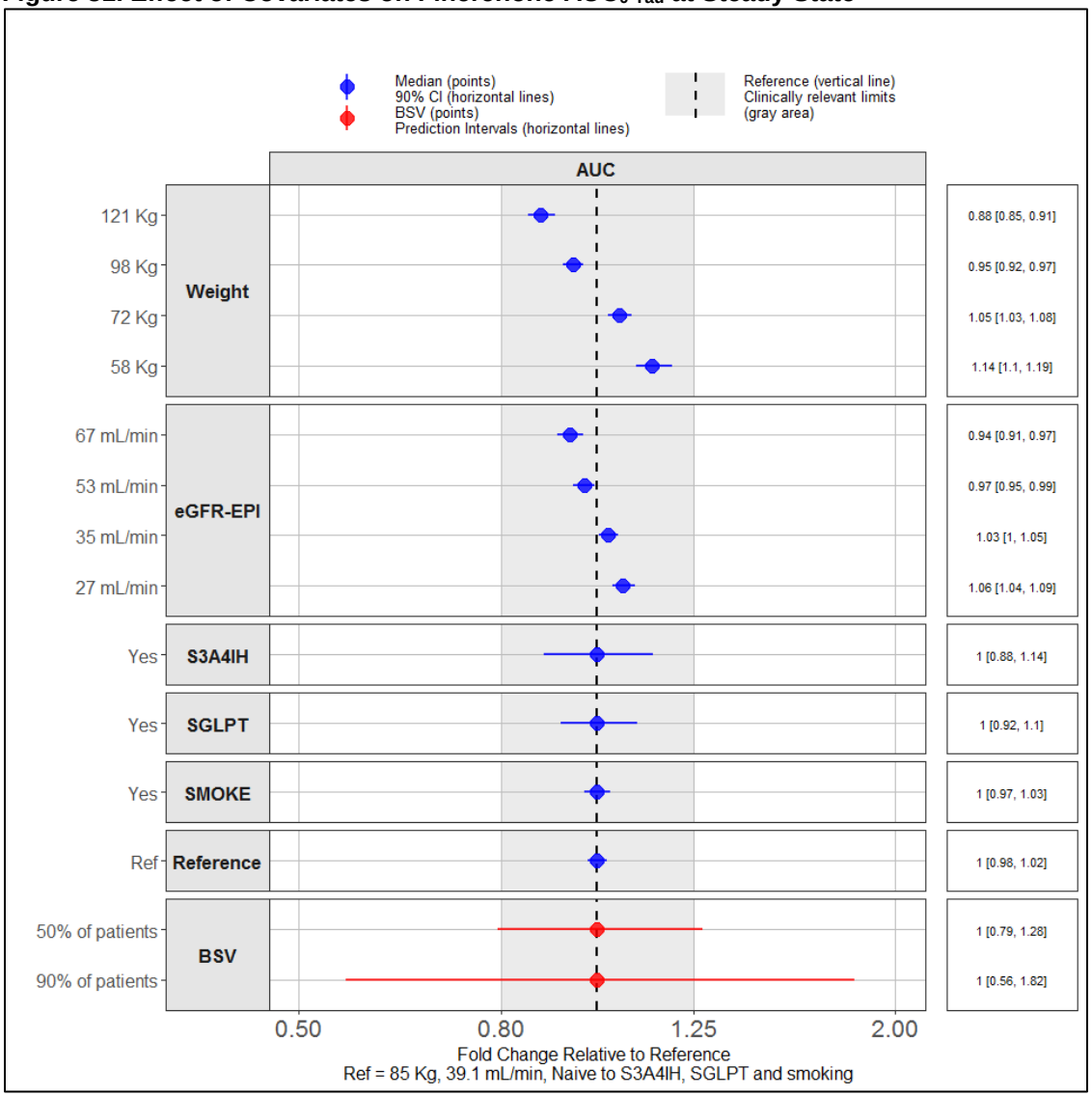
Table 142. Parameter Estimates and OFV From Reviewer's Repeat Analysis of the Applicant's Final PK Dataset

Parameters	Estimates (RSE)
OFV	32319.748
Ka (/h)	21.17 (12%)
CL (L/h)	25.63 (2%)
Vc (L)	93.59 (2%)
Q (L/h)	0.292 (NA%)
Vp (L)	239 (NA%)
ALAG1 (h)	0.215 (NA%)
Exponent for effect of time varying eGFR-EPI on CL	0.1395 (18%)
Fractional decrease of CL for use of strong CYP3A4 inhibitor	-0.1678 (42%)
Fractional decrease of F1 for use SGLT inhibitor >50%	-0.1877 (24%)
Fractional decrease of F1 for current or former smokers	-0.1244 (16%)
Allometric exponent for effect of weight on CL	0.3493 (13%)
Allometric exponent for effect of weight on Vc	0.6524 (14%)
BSV CL (%CV)	0.149 (17%)
BSV F1 (%CV)	0.3231 (5%)
Scaling factor of ETA CL to ETA Vc	-1.359 (35%)
Proportional residuals (%CV)	0.5492 (1%)

Source: Reviewer's analysis
Abbreviations: BSV, between subject variability; CL, clearance; CV, coefficient of variation; CYP, cytochrome P450; OFV, l kelihood ratio test; PK, pharmacokinetic; RSE, relative standard error; SGLT, sodium-glucose linked transporter

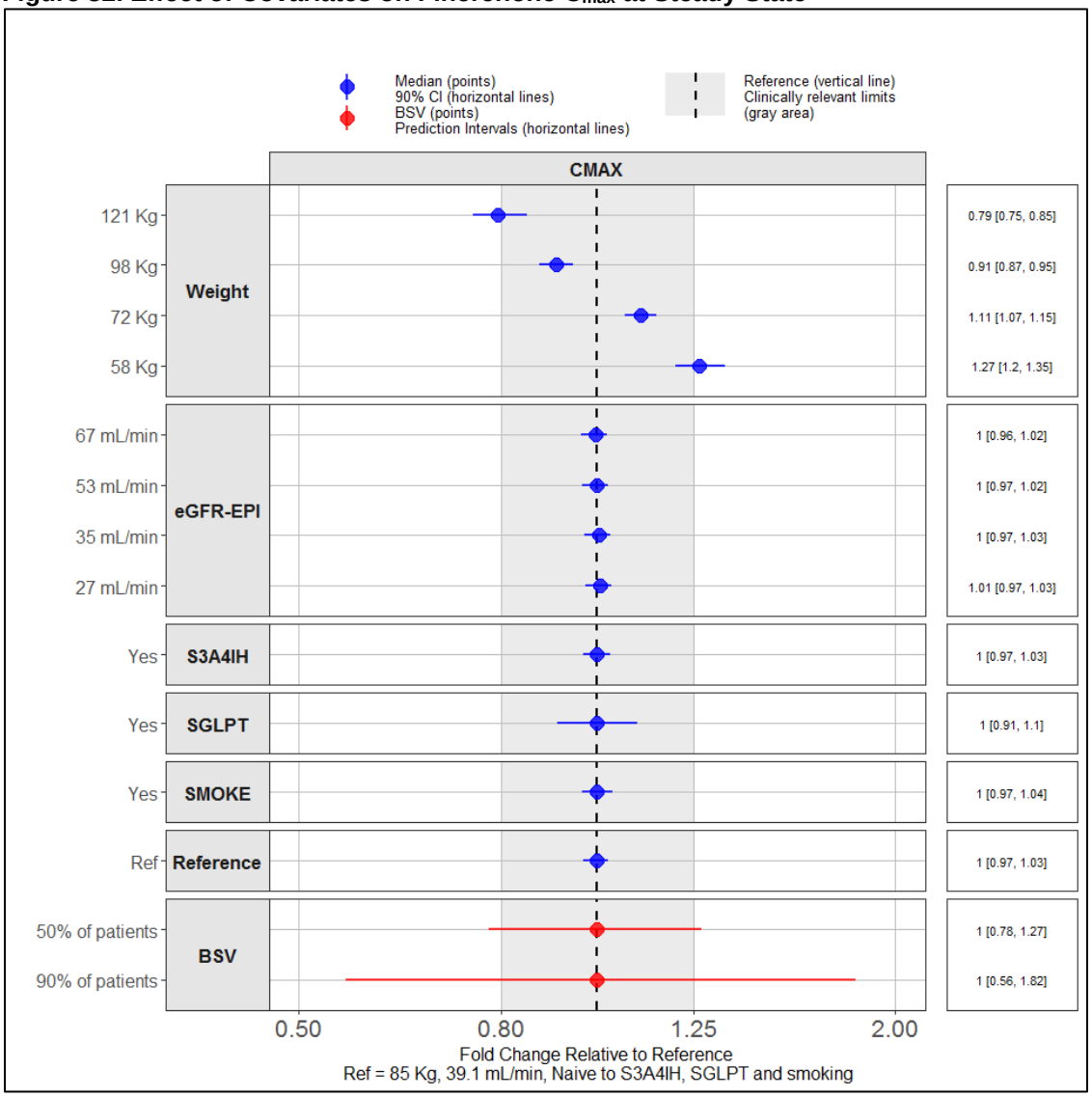
Figure 31 and Figure 32 show the predicted impact of covariates on AUC and C_{max} at steady state. Except for the impact of body weight on C_{max}, no other covariate had a clinically meaningful impact on finerenone exposure. Subjects with body weights greater than the 95th percentile (121 Kg) may have a significantly lower C_{max} compared to subjects with body weights around the mean (85 Kg).

Figure 31. Effect of Covariates on Finerenone $AUC_{0\text{-}Tau}$ at Steady State



Source: Reviewer's analysis
Abbreviations: AUC, area under the curve; BSV, between subject variability; CI, confidence interval; eGFR, estimated glomerular filtration rate

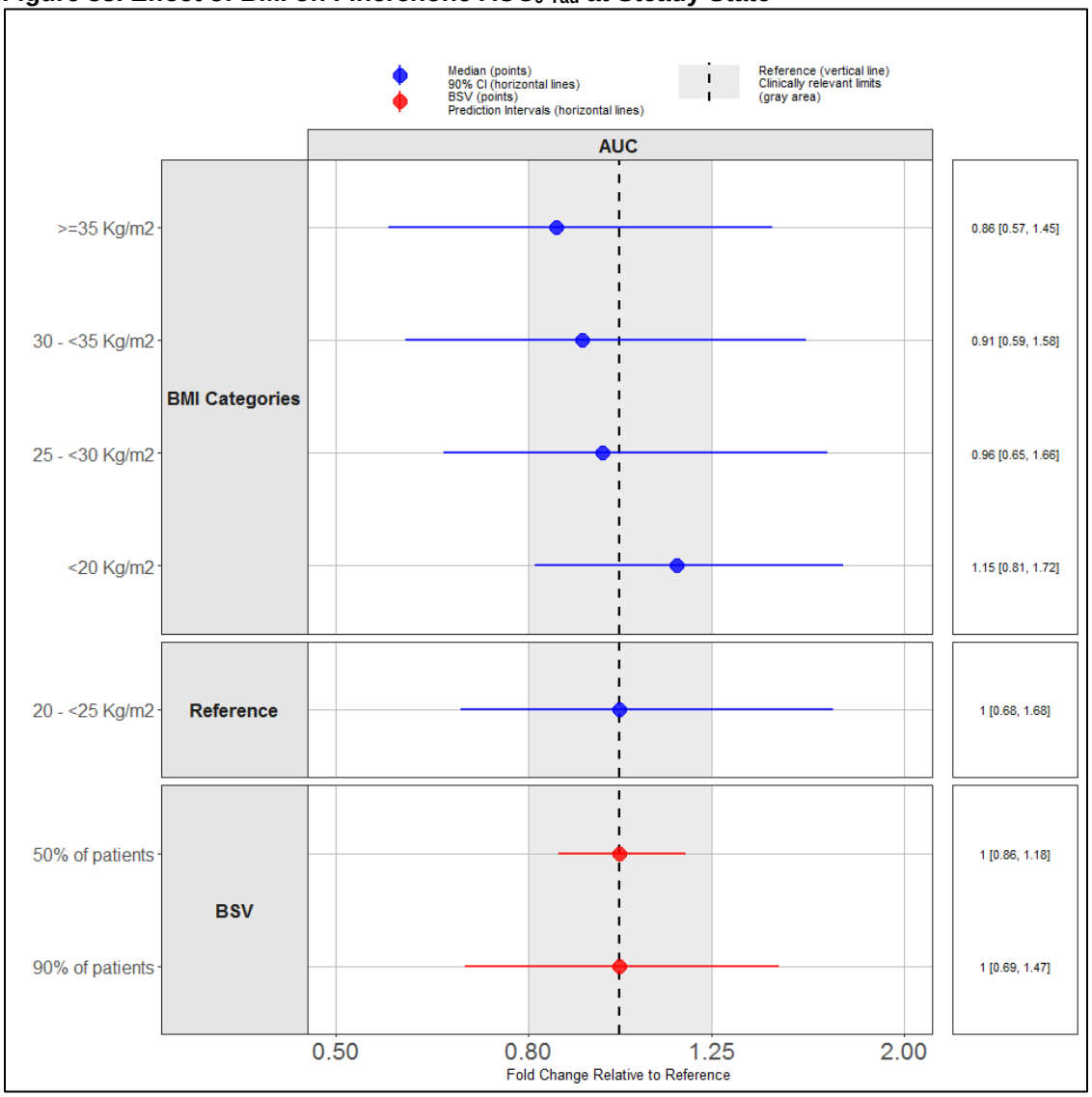
Figure 32. Effect of Covariates on Finerenone C_{max} at Steady State



Source: Reviewer's analysis
Abbreviations: BSV, between subject variability; CI, confidence interval; eGFR, estimated glomerular filtration rate

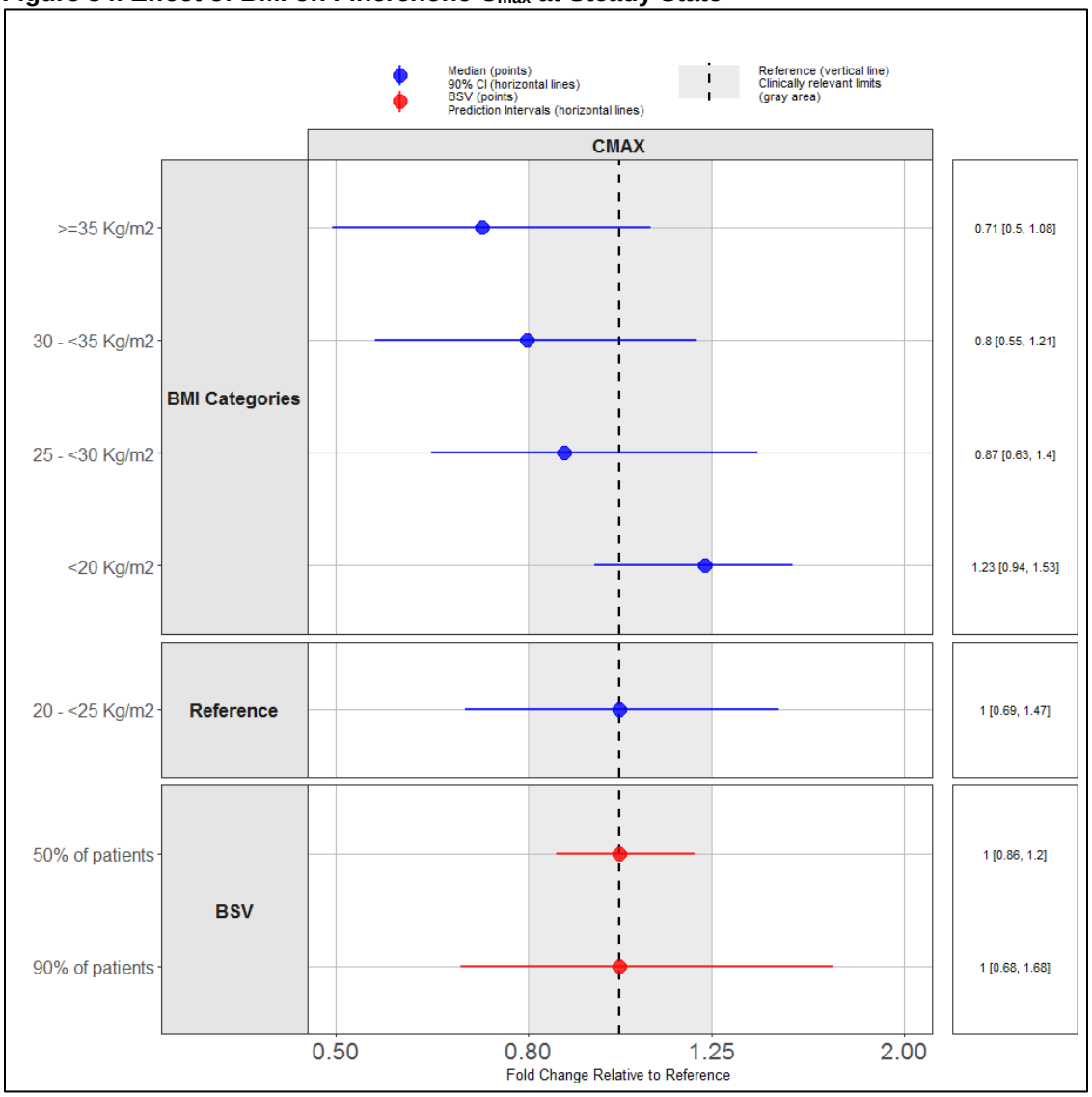
Figure 33 and Figure 34 shows the impact of BMI on finerenone AUC and C_{max}, respectively at steady state. The impact of BMI on C_{max} is observed in patients with BMI>=35 Kg/m^2. In these patients, average C_{max} is less than 0.8 folds of C_{max} in reference patients with BMIs of 20 to 25 Kg/m^2.

Figure 33. Effect of BMI on Finerenone $AUC_{0\text{-}Tau}$ at Steady State



Source: Reviewer's analysis
Abbreviations: AUC, area under the curve; BMI, body mass index; BSV, between subject variability; CI, confidence interval

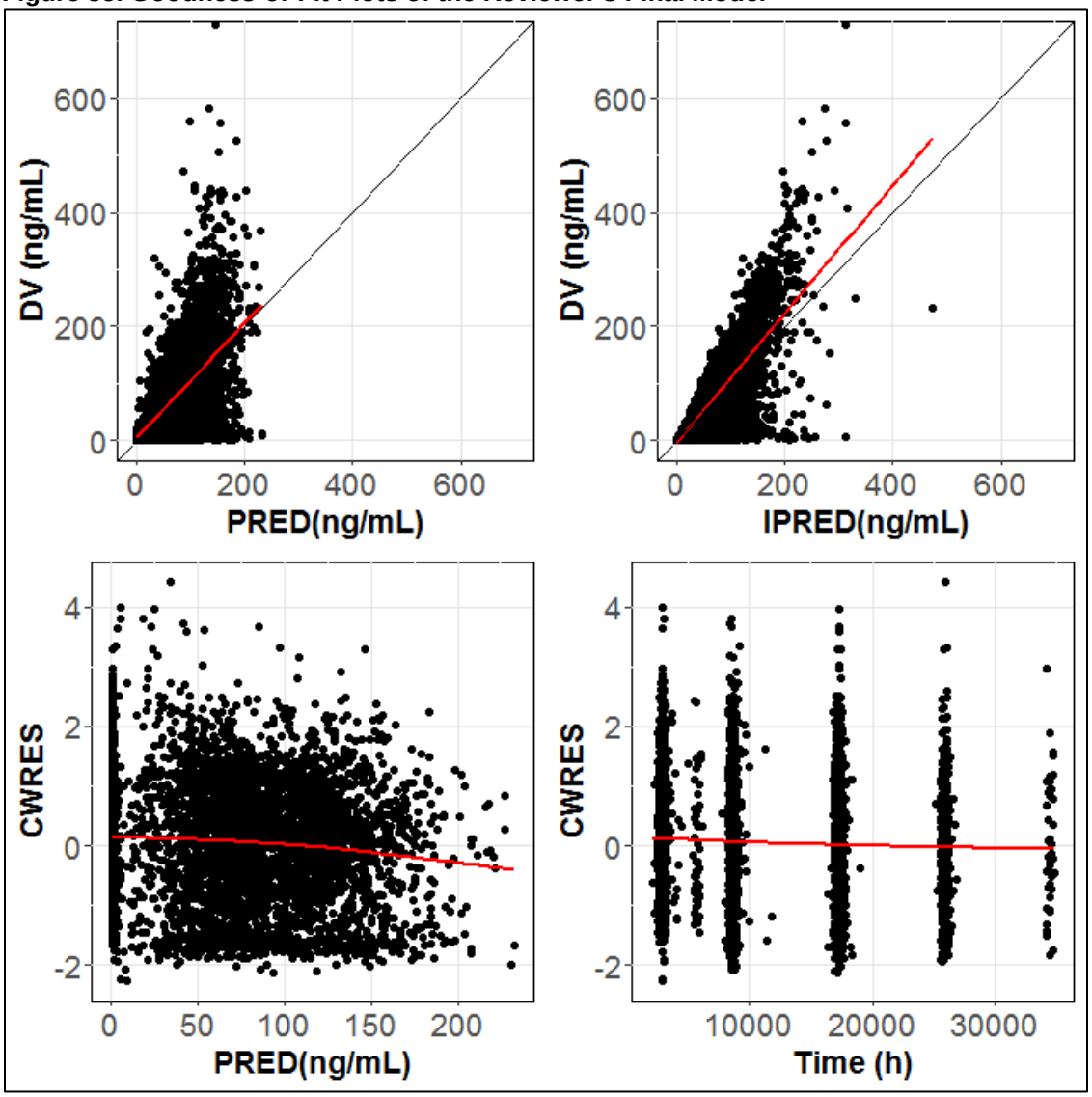
Figure 34. Effect of BMI on Finerenone C_{max} at Steady State



Source: Reviewer's analysis
Abbreviations: BMI, body mass index; BSV, between subject variability; CI, confidence interval

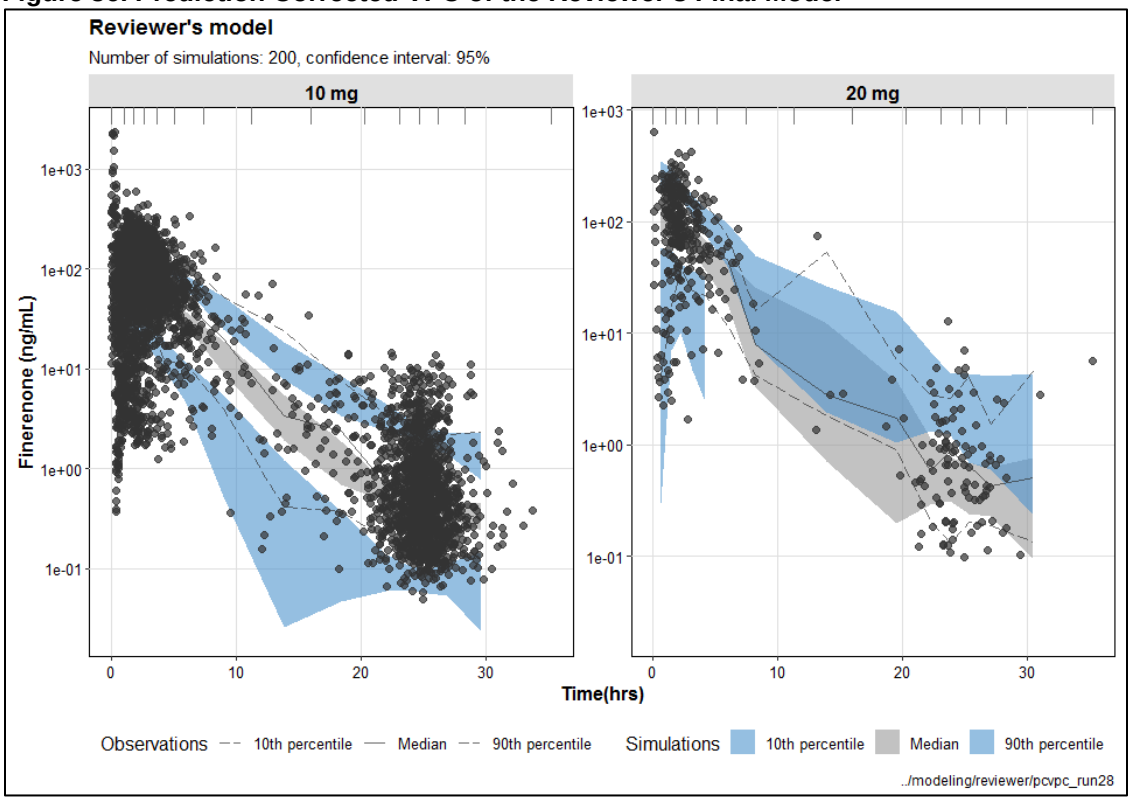
Figure 35 and Figure 36 show goodness of fit plots and prediction corrected VPC for the reviewer's final model.

Figure 35. Goodness-of-Fit Plots of the Reviewer's Final Model



Source: Reviewer's analysis
Abbreviations: CWRES, weighted population residuals; DV, observations; PRED, predicted

Figure 36. Prediction Corrected VPC of the Reviewer's Final Model



Source: Reviewer's analysis
Abbreviations: VPC, visual predictive check

Reviewer's Conclusion

Fewer covariates relationships were identified by the reviewer's model as compared to the Applicant's final model. Still, model diagnostics indicate that both models describe the data adequately.

The reviewer's model avoids including correlated covariates into the model thus preventing bias and poor precision of parameter estimates. The reviewer's model identified use of strong CYP3A4 inhibitors to be a significant covariate for CL/F. This is consistent with the results of a dedicated drug-drug interaction study of finerenone with CYP3A4 inhibitors. The Applicant's model did not identify use of strong CYP3A4 inhibitors as a covariate on CL/F.

The identified parameter-covariate relationships do not appear to have a clinically meaningful impact on finerenone exposure (C_{max} and AUC). The impact of body weight is manifested as an effect of BMI on finerenone C_{max}; however, the changes are not clinically relevant.

14.3.2. Exposure-vs-Serum Potassium Response

14.3.2.1. Review Summary

The Applicant's exposure-response (ER) analyses for serum potassium are acceptable for characterizing serum potassium response during treatment with finerenone. The serum potassium time-profile was described by an indirect response model parameterized in baseline potassium level (BSL), disease progression slope (TSLOPE), zero-order rate constant of potassium

production ($\boldsymbol{K_{in}}$),first order rate constant of potassium elimination ($\boldsymbol{K_{out}}$), and drug effect ($\boldsymbol{DE} = \frac{\boldsymbol{Emax} \times \boldsymbol{AUCss^{\gamma}}}{\boldsymbol{IC50} + \boldsymbol{AUCss^{\gamma}}}$). $\boldsymbol{K_{out}}$ was not estimated but was derived as ratio of $\boldsymbol{K_{in}}$ to BSL ($\boldsymbol{K_{out}} = \frac{\boldsymbol{K_{in}}}{\boldsymbol{BSL}}$).

Physiologically, finerenone, a mineralocorticoid receptor antagonist, elevate serum potassium levels through inhibiting its elimination. Therefore, in the model, finerenone increased potassium level through decreasing $\boldsymbol{K_{out}}$, i.e. $\boldsymbol{K'_{out}} = \boldsymbol{K_{out}} \times \boldsymbol{DE}$. The following parameter-covariate relationships were identified: BSL decreased with increasing baseline eGFR-EPI and also was lower in Japanese subjects compared to the overall population; TSLOPE increased with increasing BSL and with increasing Urine-Albumin Creatinine ratio at baseline (UACR0), also TSLOPE was higher with finerenone compared to placebo treatment. Baseline eGFR-EPI was also a covariate on Emax, with Emax decreasing with increasing baseline eGFR-EPI. E_{max} increased with increasing UACR0 and was lower in female compared to male subjects. The model parameters were precisely estimated and there was good agreement between model predicted and observed data. As a sensitivity analysis, the reviewer repeated the final model evaluation using the exposure parameter (AUC_{ss}) derived from the reviewer's final PopPK model described in Section 14.3.1. The repeat evaluation also indicated good agreement between model predicted and observed data.

14.3.2.2. Applicant's Exposure-Response Analyses

The Applicant developed the ER model for serum potassium in several steps using data from a phase 2 (ARTS-DN) and a phase 3 study (FIDELIO-DKD). First, the model was developed using data from the ARTS-DN study (Hence forth called ARTS-DN model). The ARTS-DN model was applied to the data from FIDELIO-DKD to evaluate its predictive performance. The ARTS-DN model failed to predict the FIDELIO-DKD data. The failure to predict FIDELIO-DKD data were attributed to higher mean and between subject variability of baseline serum potassium in the FIDELIO-DKD study compared to ARTS-DN study. The second step was to update the ARTS-DN model using data from FIDELIO-DKD only. The updated model (henceforth called FIDELIO-DKD model) had a different structural model compared to the ARTS-DN model: a disease progression model term (TSLOPE) was introduced; the DE was modelled as an Emax model instead of a log-linear model and AUCss instead of concentration was used as the driver of DE. In the FIDELIO-DKD model, BSL and K_{in} were re-estimated and new parameter-covariate relationships were investigated.

A brief description of the FIDELIO-DKD study is given in Table 139. Summary statistics of the baseline subject characteristics for subjects included in the ER dataset are given in Table 143. Mean age, weight and observed baseline potassium levels were comparable between the treatment groups.

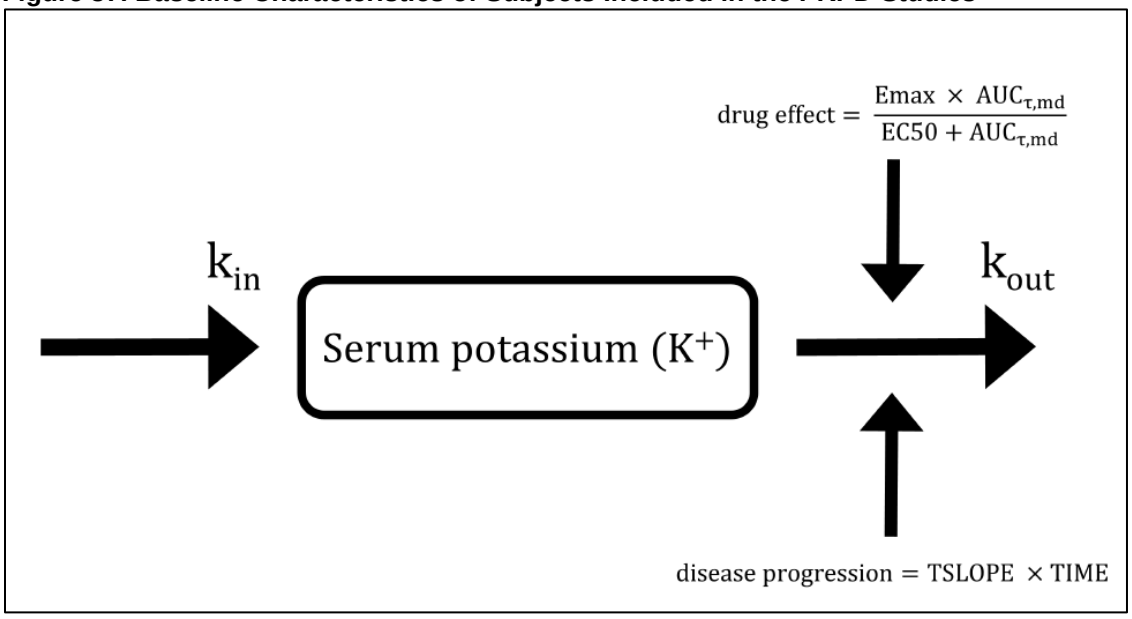
Table 143. Baseline Covariates of Subjects Included in the PKPD Modeling

Characteristics	Starting Dose			P-Value
	10 mg N=2622	20 mg N=211	Placebo N=2841	
Measurement (mean (SD))				
Age (years)	65.57 (9.01)	63.85 (7.86)	65.67 (9.16)	0.018
Weight (kg)	86.68 (19.81)	88.12 (19.32)	87.53 (20.14)	0.225
BMI (kg/m^2)	31.12 (6.04)	31.18 (5.76)	31.09 (5.99)	0.973
Baseline Potassium (mmol/L) (Central laboratory)	4.37 (0.46)	4.34 (0.45)	4.38 (0.46)	0.521
Baseline Potassium (mmol/L) (Local laboratory)	4.45 (0.49)	4.39 (0.60)	4.45 (0.49)	0.172
UACR0	1191.72 (1044.51)	1109.84 (931.49)	1210.20 (1052.18)	0.371
Baseline eGFR-EPI (mL/min/1.73 m^2)	42.69 (11.18)	65.15 (9.57)	44.32 (12.57)	<0.001
Sex (n (%))				
Female	822 (31.4)	58 (27.5)	811 (28.5)	0.058
Male	1800 (68.6)	153 (72.5)	2030 (71.5)	
Race (n (%))				
Black/African American	130 (5.0)	10 (4.7)	124 (4.4)	0.099
Japanese	67 (2.6)	11 (5.2)	76 (2.7)	
Korean	9 (0.3)	2 (0.9)	7 (0.2)	
Not reported or multiple	779 (29.7)	48 (22.7)	819 (28.8)	
White	1637 (62.4)	140 (66.4)	1815 (63.9)	
CYP3A4 inducer use (n (%))				
Moderate Cyp ind <50%	117 (4.5)	11 (5.2)	152 (5.4)	0.516
Moderate Cyp ind >50%	9 (0.3)	0 (0.0)	20 (0.7)	
None	2111 (80.5)	175 (82.9)	2267 (79.8)	
Strong Cyp ind <50%	27 (1.0)	1 (0.5)	29 (1.0)	
Strong Cyp ind >50%	3 (0.1)	1 (0.5)	4 (0.1)	
Unclassified Cyp ind <50%	108 (4.1)	6 (2.8)	104 (3.7)	
Unclassified Cyp ind >50%	18 (0.7)	0 (0.0)	17 (0.6)	
Weak Cyp ind <50%	129 (4.9)	6 (2.8)	134 (4.7)	
Weak Cyp ind >50%	100 (3.8)	11 (5.2)	114 (4.0)	
CYP3A4 inhibitor use (n (%))				
Moderate Cyp inh <50%	99 (3.8)	12 (5.7)	106 (3.7)	0.282
Moderate Cyp inh >50%	53 (2.0)	7 (3.3)	60 (2.1)	
None	671 (25.6)	63 (29.9)	699 (24.6)	
Strong Cyp inh <50%	63 (2.4)	1 (0.5)	59 (2.1)	
Strong Cyp inh >50%	19 (0.7)	1 (0.5)	22 (0.8)	
Unclassified Cyp inh <50%	39 (1.5)	3 (1.4)	49 (1.7)	
Unclassified Cyp inh >50%	39 (1.5)	2 (0.9)	36 (1.3)	
Weak Cyp inh <50%	235 (9.0)	16 (7.6)	314 (11.1)	
Weak Cyp inh >50%	1404 (53.5)	106 (50.2)	1496 (52.7)	

Source: Reviewer's analysis
Abbreviations: BMI, body mass index; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; PKPD, pharmacokinetic pharmacodynamic; UACR, Urine-Albumin Creatinine ratio

The Applicant found that the basic indirect response PK-PD model, as shown in Figure 37, was the most parsimonious model to characterize the effects of finerenone on serum potassium levels.

Figure 37. Baseline Characteristics of Subjects Included in the PKPD Studies



source: Applicant's population PKPD report (#20955 / R-13543, pages 48)
Abbreviations: AUC, area under the curve; PKPD, pharmacokinetic pharmacodynamic

A stepwise covariate model building procedure (guided by graphical exploration) was used to assess the covariates of the ER model parameters. The parameter estimates of the final potassium ER model are given in Table 144. The parameter-covariate relationships for BSL are as given in Equation 1, where $\theta_{pop,BSL}$ is the population estimate for BSL, EGFREPI0 is the baseline eGFR-EPI in ml/min/1.73m2, $\theta_{EGFR,BSL}$ is the estimated power of the covariate effect of baseline EGFR-EPI on BSL, $\theta_{JAP,BSL}$ is the estimated effect of Japanese ethnicity on BSL and JAP is an indicator variable that is 1 for subjects with a Japanese ethnicity and 0 otherwise.

Table 144. Parameter Estimates of the Final Indirect ER Model for Effect of Finerenone on HCT in PV Patients

Parameter Name	Estimate	SE	RSE (%)	95% CI
$\theta_{pop,BSL}$, BSL (mmol/L)	4.50	0.00628	0.140	(4.48, 4.51)
$\theta_{pop,local}$, Relative difference local lab versus central lab	0.0204	0.000459	2.25	(0.0195, 0.0213)
$\theta_{pop,kin}$, k_{in} (mmol/L*hr)	0.00981	0.00140	14.2	(0.00707, 0.0125)
$\theta_{pop,EMAX}$, E_{max}	0.0905	0.0147	16.2	(0.0618, 0.119)
$\theta_{pop,EC50}$, EC50 (mg*hr/L)	0.512	0.170	33.3	(0.178, 0.846)
$\theta_{pop,TSLOPE_{placebo}}$ TSLOPE in placebo arm (/year)	0.00412	0.000587	14.2	(0.00297, 0.00527)
$\theta_{pop,TSLOPE_{active}}$ TSLOPE in active treatment arm (/year)	0.00161	0.000401	24.9	(0.000823, 0.00239)
$\theta_{JAP,\sigma}$, Relative σ with Japanese ethnicity (%)	87.0	3.17	3.64	(80.8, 93.2)
$\theta_{JAP,BSL}$, Relative difference in BSL with Japanese ethnicity (%)	-3.62	0.364	10.1	(-4.34, -2.91)
$\theta_{EGFR,BSL}$, Effect of EGFREPI0 on BSL	-0.0429	0.00344	8.02	(-0.0497, -0.0362)
$\theta_{BSL,TSLOPE}$, Effect of BSL on TSLOPE (L/mmol)	1.60	0.172	10.8	(1.26, 1.94)
$\theta_{UACR,TSLOPE}$, Effect of UACR0 on TSLOPE (g/mg)	0.00114	0.000223	19.6	(0.000701, 0.00157)
$\theta_{EGFR,EMAX}$, Effect of EGFREPI0 on Emax	-0.305	0.0719	23.6	(-0.446, -0.164)
$\theta_{UACR,EMAX}$, Effect of UACR0 on Emax (g/mg)	0.0000931	0.0000220	23.7	(0.0000499, 0.000136)
$\theta_{SEX,EMAX}$, Effect of SEX on Emax	-0.143	0.0288	20.1	(-0.200, -0.0867)
Variability	**Estimate**	**SE**	**RSE (%)**	**%CV**
ω^2 Exponential BSL	0.00717	0.000174	2.43	8.48
ω^2 Proportional E_{max}	1.49	0.152	10.2	185
ω^2 Covariance BSL/E_{max}	-0.0385	0.00417	10.8	-
Shape parameter Box-Cox transformation exponential IIV on BSL	-1.61	0.280	17.4	-
Residual Error	**Estimate**	**SE**	**RSE (%)**	**stDev**
σ^2 - scalar of residual error	0.00447	0.0000440	0.986	0.0668
v - degrees of freedom of t-distributed residual error	6.60	0.119	1.81	-

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI; %CV is calculated as sqrt(exp(OM)-1)*100 in case of exponential variability or sqrt(OM)/TH*100 in case of additive variability, or presents the correlation coefficient (OMx,y / (sqrt(exp(OMx)-1) * sqrt(exp(OMy)-1))) for the covariance between parameters; StDev is calculated as sqrt(SIG), if SIG is defined already as StDev it will be the same as estimate

Source: Applicant's population PKPD report (#20955 / R-13543, pages 51)
Abbreviations: BSL, baseline potassium level; ER, exposure-response; RSE, relative standard error; SE, standard error; TSLOPE, disease progression slope; HCT, hematocrit; PV, polycythemia vera

Equation 1. Equation Describing Covariate Effects on Baseline Potassium Concentration

$$\theta_{BSL} = \theta_{pop,BSL} \cdot \left(\frac{EGFREPI0}{45}\right)^{\theta_{EGFR,BSL}} \cdot \left(1 + \frac{\theta_{JAP,BSL}}{100} \cdot JAP\right)$$

Source: Applicant's population PKPD report (#20955 / R-13543, pages 47)
Abbreviations: BSL, baseline potassium level; eGFR, estimated glomerular filtration rate

The parameter-covariate relationships for E_{max} are as given in Equation 2 where $\theta_{pop,EMAX}$ is the population estimate for E_{max}, EGFREPI0 is the baseline eGFR-EPI, $\theta_{EGFR,EMAX}$ is the estimated power of the covariate effect of baseline EGFR-EPI on Emax, $\theta_{SEX,EMAX}$ is the estimated effect of SEX on E_{max}, SEX is an indicator variable that is 1 for female subjects and 0 for male subjects, $\theta_{UACR,EMAX}$ is the estimated slope of covariate effect of baseline UACR on E_{max} and UACR0 is the baseline UACR in mg/g

Equation 2. Equation Describing Covariate Effects on E_{max}

$$\theta_{EMAX} = \theta_{pop,EMAX} \cdot \left(\frac{EGFREPI0}{45}\right)^{\theta_{EGFR,EMAX}} \cdot (1 + \theta_{SEX,EMAX} \cdot SEX) \cdot (1 + \theta_{UACR,EMAX} \cdot (UACR0 - 800))$$

Source: Applicant's population PKPD report (#20955 / R-13543, pages 47)
Abbreviations: eGFR, estimated glomerular filtration rate; UACR, urine-albumin creatinine ratio

The parameter-covariate relationships for TSLOPE are as given in Equation 3, where $\theta_{pop,TSLOPE_{active}}$ and $\theta_{pop,TSLOPE_{placebo}}$ are the population estimate for TSLOPE for the active treatment and the placebo treatment arm, respectively, $\theta_{UACR,TSLOPE}$ is the estimated effect of baseline UACR on TSLOPE, $\theta_{BSL,TSLOPE}$ is the estimated effect of BSL on TSLOPE, and BSLi is the individual post hoc estimate of the baseline serum potassium parameter (BSL) in mmol/L.

Equation 3. Equation Describing Covariate Effects on TSLOPE

$$\theta_{TSLOPE} = \theta_{pop,TSLOPE_{active}} \cdot (1 + \theta_{UACR,TSLOPE} \cdot (UACR0 - 800)) \cdot (1 + \theta_{BSL,TSLOPE} \cdot (BSL_i - 4.4)) \quad \text{Placebo treatment arm}$$

$$\theta_{TSLOPE} = \theta_{pop,TSLOPE_{placebo}} \cdot (1 + \theta_{UACR,TSLOPE} \cdot (UACR0 - 800)) \cdot (1 + \theta_{BSL,TSLOPE} \cdot (BSL_i - 4.4)) \quad \text{Active treatment arm}$$

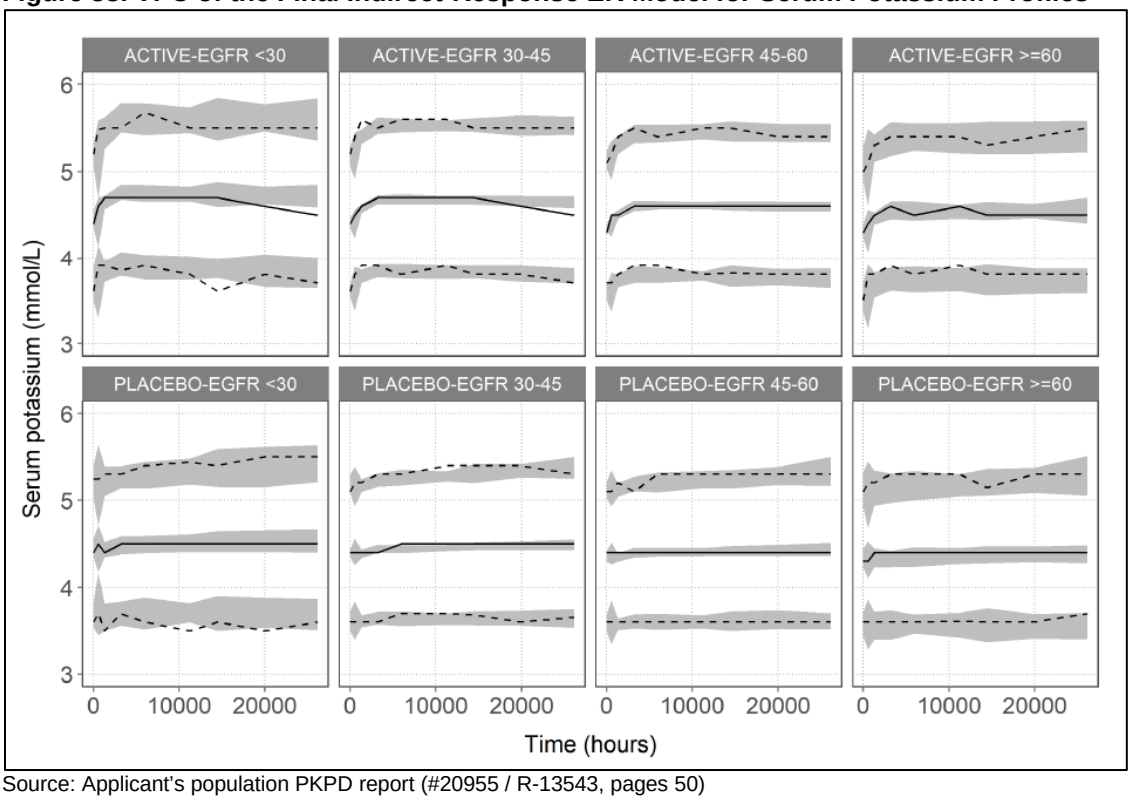
Source: Applicant's population PKPD report (#20955 / R-13543, pages 47)
Abbreviations: BSL, baseline potassium level; TSLOPE, disease progression slope; UACR, urine-a bumin-creatinine ratio

All parameters were estimated with good precision as the RSE was <50% for all parameters. The typical value of E_{max} on K_{out} in the turnover model corresponds to a maximum increase of serum potassium by 9.95%, which amounts to an increase of 0.44 mmol/L for a patient with serum potassium baseline of 4.4 mmol/L. The model estimated a slower rate of disease progression (TSLOPE) in the active treatment arm compared to the placebo arm: 0.412% versus 0.161% per

year increase in serum potassium, respectively, for patients with baseline serum potassium of 4.4 mmol/L and UACR0 of 800 mg/g. The disease progression rate is also affected by baseline serum potassium (16% faster progression with each 0.1 mmol/L increase in baseline serum potassium) and baseline UACR (11.4% faster progression with each 100 mg/g increase of baseline UACR)

The visual predictive check (VPC) of the final ER model is shown in Figure 38. The figure shows good agreement between observed and predicted serum potassium profiles for subjects in finerenone and placebo treatment groups and stratified by renal functional status.

Figure 38. VPC of the Final Indirect-Response ER Model for Serum Potassium Profiles



Source: Applicant's population PKPD report (#20955 / R-13543, pages 50)
Abbreviations: eGFR, estimated glomerular filtration rate; ER, exposure-response; VPC, visual predictive check

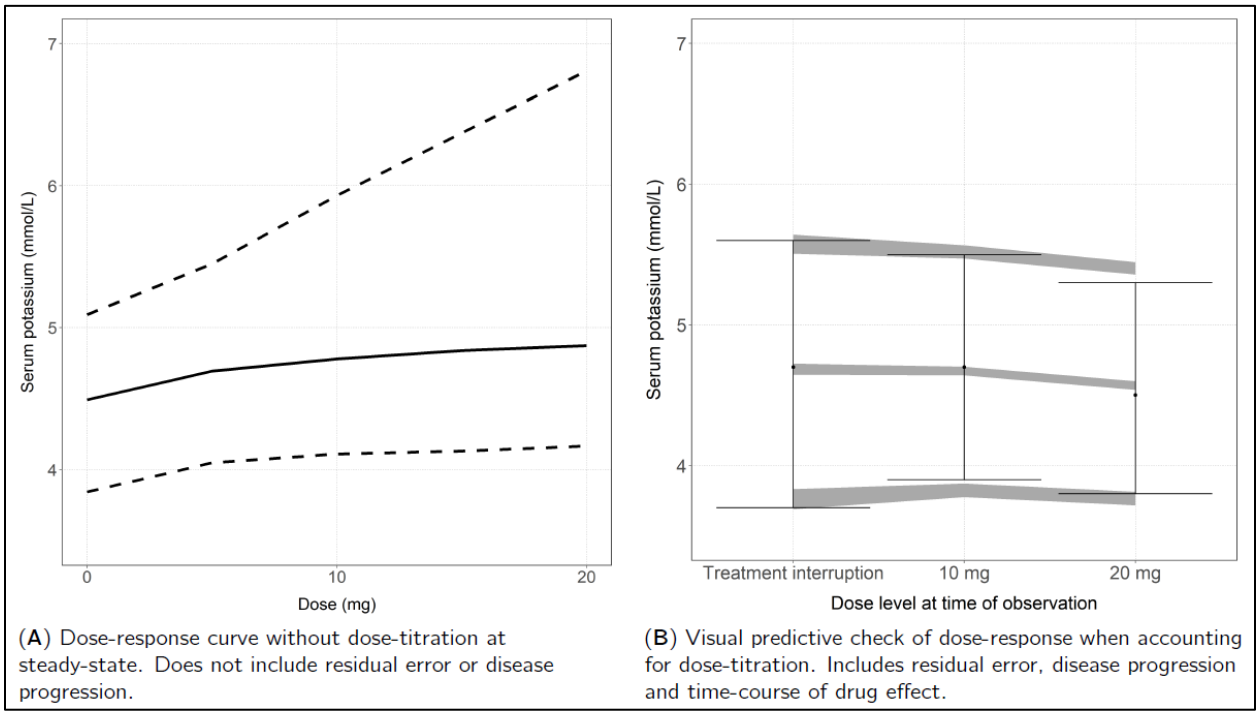
The Applicant's final ER model for serum potassium had good predictive performance for proportion of subjects with hyperkalemia in the FIDELIO-DKD study. In the predictive performance analyses, the model was able to predict proportions with hyperkalemia by across different covariates as follows: Proportions of subjects with hyperkalemia increased with increasing baseline potassium levels; the proportions decreased with increasing baseline eGFR-EPI; and increased with increasing UACR.

The final ER model was also able to characterize the dosing patterns (i.e., proportions of patients on 10 mg, 20 mg, and treatment interruptions over-time) in the FIDELIO-DKD study. By simulating the dose-titration decisions based on simulated serum potassium levels, the final ER models was able to re-create the observed finerenone dosing patterns observed in the FIDELIO-DKD study.

Monte Carlo simulations using the Applicant's final ER model for serum potassium, without dose titration and interruptions indicated that serum potassium increased with increasing

finerenone dose, approaching plateau at 20 mg dose (Figure 39). However, with dose interruptions and titration as practiced in the FIDELIO-DKD, the 20 mg dose was associated with lower serum potassium levels compared to the 10 mg dose.

Figure 39. The Impact of Dose-Titration on the Observed Dose-Response of Finerenone on Serum Potassium in the FIDELIO-FKD.



(**A**) Dose-response curve without dose-titration at steady-state. Does not include residual error or disease progression.

(**B**) Visual predictive check of dose-response when accounting for dose-titration. Includes residual error, disease progression and time-course of drug effect.

Source: Applicant's population PKPD report (#20955 / R-13543, page 57)
Panel A illustrates the dose-response relationship without accounting for dose-titration. Shown are the median (solid line) and 90% prediction interval (dashed lines) of 10,000 simulated individual predicted serum potassium levels (including inter-individual variability, but not residual error) with drug effect at steady state, ignoring the impact of disease progression. All simulated patients have typical covariates (male sex, non-Japanese ethnicity, baseline eGFR-EPI of 45 ml/min/1.73m2, baseline UACR of 800 mg/g) and a typical finerenone clearance of 28.0 L/h). Panel B shows a visual predictive check of the dose-response of finerenone on serum potassium. Observed data are shown as black points (median) and error bars (depicting the 5th and 95th percentiles), while the grey areas indicate the 99% variability-based prediction interval of simulations that include dose-titration (excluding parameter uncertainty)

14.3.2.3. Applicant's Evaluation of Initiation and Titration Thresholds

The Applicant used the final ER model to evaluate serum potassium thresholds for initiation of finerenone treatment and for titration from 10 mg to 20 mg. In the FIDELIO-DKD study, the serum potassium threshold for initiation and titration was ≤ 4.8 mmol/L. The Applicant evaluated the relative risk of hyperkalemia for the following combinations of initiation and titration thresholds (Initiation -> titration): 4.8 ->4.8; 4.8 ->5.0; 5.0 ->4.8; and 5.0 ->5.0. Several clinical endpoints were used for this evaluation including but not limited to: Proportions with hyperkalemia (>5.5 mmol/L); frequency of temporary treatment interruptions; and relative risk of hyperkalemia (>5.5 mmol/L). The results of this analysis are given in Table 145. The results show that the initiation threshold of 5.0 mmol/L and titration threshold of 4.8 mmol/L have the smallest relative risk of hyperkalemia (finerenone versus placebo). With this combination, subjects with serum potassium $\leq 5.0\ mmol/L$ can be initiated on 10 mg finerenone treatment, but cannot be titrated to 20 mg unless their serum potassium levels decreases to $\leq 4.8\ mmol/L$.

Table 145. Influence of Serum Potassium Thresholds for Inclusion and Up-Titration in a Simulation Scenario Similar to Study 16244 (FIDELIO-DKD)

	Inclusion threshold (mmol/L)			
	≤4.8		≤5.0	
	Up-titration threshold (mmol/L)			
	≤4.8	≤5.0	≤4.8	≤5.0
Potassium-related inclusion eligibility (%)	81.8 (80.9-82.7)	81.8 (80.9-82.7)	91.3 (90.4-92.2)	91.3 (90.4-92.2)
Frequency of temporary treatment interruption (%)	8.54 (6.96-10.1)	9.09 (7.39-10.8)	10.6 (8.85-12.3)	11.2 (9.28-13.0)
Frequency of 10 mg dose level (%)	38.6 (36.7-40.6)	35.2 (33.3-37.1)	39.3 (37.5-41.2)	35.6 (33.8-37.3)
Frequency of 20 mg dose level (%)	52.8 (49.9-55.7)	55.7 (52.7-58.7)	50.1 (47.1-53.1)	53.3 (50.2-56.3)
Average dose level (mg)	14.4 (14.0-14.9)	14.7 (14.2-15.1)	13.9 (13.5-14.4)	14.2 (13.7-14.7)
Hyperkalemia >5.5 mmol/L on finerenone (%)	20.3 (17.9-22.6)	20.9 (18.2-23.5)	23.4 (20.8-25.9)	24.0 (21.2-26.8)
Hyperkalemia >5.5 mmol/L on placebo (%)	9.42 (7.99-10.9)	9.41 (8.02-10.8)	12.9 (11.3-14.4)	12.9 (11.4-14.3)
Hyperkalemia >6.0 mmol/L on finerenone (%)	4.50 (3.61-5.39)	4.83 (3.92-5.74)	5.51 (4.54-6.47)	5.88 (4.91-6.85)
Hyperkalemia >6.0 mmol/L on placebo (%)	1.71 (1.03-2.40)	1.71 (1.05-2.38)	2.61 (1.77-3.46)	2.62 (1.77-3.48)
Relative Risk of hyperkalemia >5.5 mmol/L	2.16 (1.76-2.56)	2.23 (1.82-2.63)	1.82 (1.55-2.10)	1.87 (1.58-2.16)
Relative Risk of hyperkalemia >6.0 mmol/L	2.75 (1.36-4.13)	2.94 (1.52-4.37)	2.16 (1.41-2.90)	2.30 (1.51-3.09)

Data are displayed as mean (95% prediction interval) of 30 iterations of the simulation. Dosing statistics are calculated across all simulated observations before the time of permanent treatment interruption. Hyperkalemia is calculated as the percentage of patients with one or more central laboratory observations >5.5 mmol/L or >6.0 mmol/L after the baseline visit.

Source: Applicant's population PKPD report (#20955 / R-13543, pages 56)

Reviewer's Comment

The Applicant's ER analyses are acceptable for drawing conclusions about exposure-response relationships for serum potassium. The model indicates that finerenone causes exposure-dependent elevations in serum potassium. The Applicant's evaluation of the potassium thresholds for titration also supports the recommended dosing instructions for finerenone with thresholds for initiation and titration being 5.0 mmol/l and 4.8 mmol/L respectively. Despite exposure-dependent risk for hyperkalemia, the Applicant did not identify concomitant CYP3A4 inhibitors to be a risk factor for hyperkalemia. This was consistent with the Applicant's PopPK model, where the CYP3A4 inhibitor category was not a covariate on PK parameters. However, the reviewer's alternative PopPK modeling identified CYP3A4 inhibitors to be a covariate of finerenone clearance which is consistent with the dedicated drug-drug interaction study that found that CYP3A4 inhibitors elevate finerenone exposure. Due to this inconsistency, the reviewer assessed the impact of concomitant CYP3A4 inhibitors on the hazard-rate of hyperkalemia.

14.3.2.4. Reviewer's Assessment of Hyperkalemia Frequencies Over Time in Subjects Taking CYP3A4 Inhibitors

Introduction

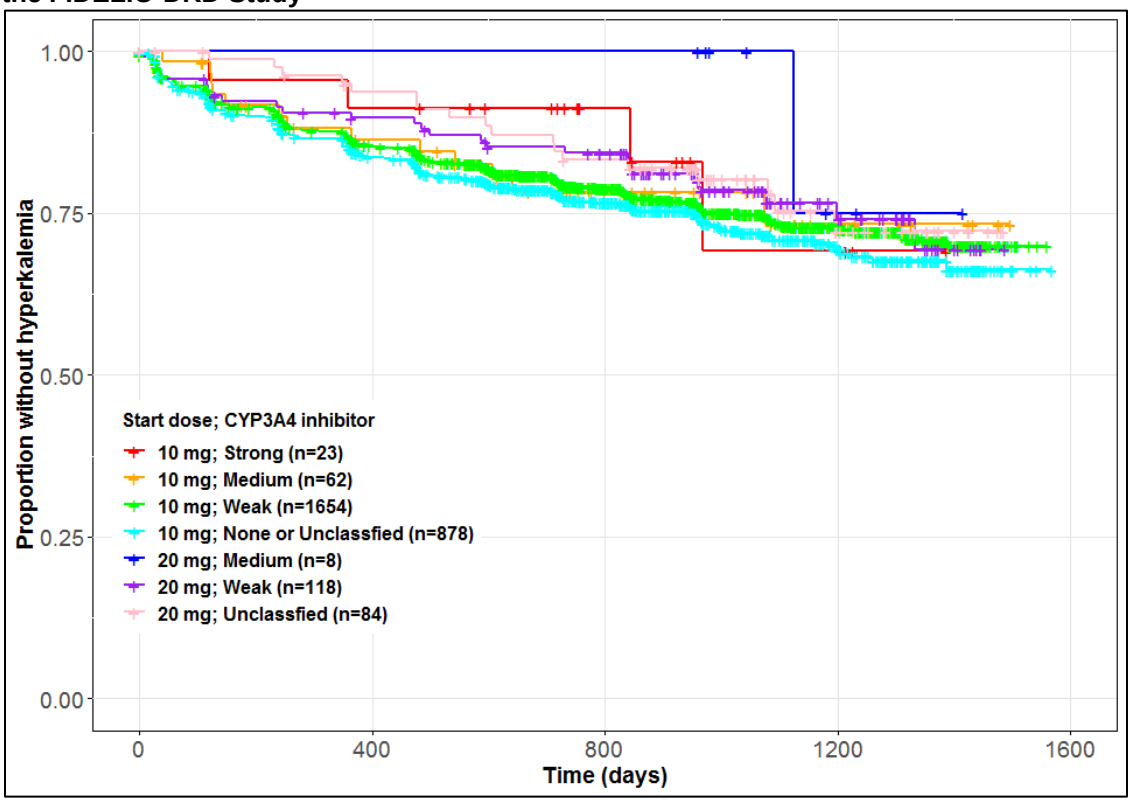
Finerenone treatment is associated with increase in serum potassium levels. In an exposure response analysis (Section 14.3.2.2), the relationship between finerenone exposure and serum potassium levels was described by an Emax model. Although a dedicated drug-drug interaction study and reviewer's alternative PopPK model indicate higher finerenone exposure in subjects on

concomitant CYP3A4 inhibitors, the Applicant's ER analysis did not identify an increased risk of hyperkalemia in subjects on these drugs. The reviewer further evaluated the risk of hyperkalemia for concomitant CY3A4 inhibitor use based off data from FIDELIO.

Kaplan-Meier Curves for Rate of Hyperkalemia Events

A time to event (TTE) analysis using Kaplan-Meier curves was performed using the same dataset used by the Applicant for ER analyses. In this TTE analysis, observed data in subjects receiving finerenone treatment were used. Hyperkalemia was defined as a serum potassium >5.5 mmol/L. The results of the analyses are shown in Figure 40. The figure shows a lower incidence of hyperkalemia in subjects who were initiated on the 20 mg dose than on the 10 mg dose. Among those initiated on the 10 mg dose, the Kaplan-Meier curves for the different strengths of CYP3A4 inhibitors overlap. This implies that concomitant CYP3A4 inhibitors did not increase the risk of hyperkalemia regardless of strength of inhibition. Of those initiated on the 20 mg dose, too few subjects were receiving concomitant moderate CYP3A4 inhibitors to use the data to draw meaningful conclusions.

Figure 40. Kaplan-Meier Curves for Time to Hyperkalemia Events During Finerenone Treatment in the FIDELIO-DKD Study



Source: Reviewer's analysis

Conclusions from the Reviewer's Analyses

Although the reviewer's PopPK analyses and the dedicated studies identified that concomitant use of CYP3A4 inhibitors increases finerenone exposure, the Applicant's PKPD analyses did not identify CYP3A4 inhibitors as covariates for any of the PKPD parameters. This may be because few subjects were taking moderate to strong inhibitors in the FIDELIO study and/or because of the large between subject variation in serum potassium levels due to the interplay of other

covariates. Based on the Applicant's analyses, in addition to finerenone exposure, other predictors of hyperkalemia are baseline potassium and disease progression. In turn, these predictors of hyperkalemia (baseline potassium, finerenone exposure and disease progression) are impacted by renal function at baseline (eGFR0). Therefore, renal function directly influences serum potassium through its organ function and indirectly through its impact on finerenone exposure.

Based on the drug-drug interaction study, it is expected that concomitant use with CYP3A4 inhibitors would increase the risk of hyperkalemia by influencing finerenone exposure. Patients on CYP3A4 inhibitors - initiating finerenone treatment- will have relatively higher finerenone exposures at steady state compared to subjects who are not on CYP3A4 inhibitors. However, based on the parameter estimates of the ER model, it would take 66 days for potassium levels to reach new steady state levels after changes in finerenone exposure. Because of the time course for finerenone-dependent effects on serum potassium (i.e., the full effect of finerenone on changes in serum potassium may not be immediate), patients on CYP3A4 inhibitors may benefit from additional monitoring of potassium levels and subsequent dose adjustment.

14.3.3. Exposure-vs-Time to Pivotal Endpoints

14.3.3.1. Review Summary

The Applicant's exposure-vs-time to pivotal endpoints analyses are acceptable for describing relationships between finerenone exposures and primary and secondary treatment outcomes. Using individual predicted finerenone concentration at the time of occurrence of events, the Applicant assessed the relationship between finerenone exposure and both the primary renal composite outcomes, and the secondary cardiovascular composite outcomes. Time to event analyses determined that a Weibull hazard model best described the time to renal composite events, and the Exponential hazard model best described the time to cardiovascular composite endpoint. In addition to finerenone exposure, the identified prognostic factors for renal composite events rates were the following: UACR, baseline eGFR-EPI, BMI, age, race/ethnicity, concomitant SGLT2 inhibitors, and hepatic impairment. Additional prognostic factors for cardiovascular events rate were UACR, time varying eGFR-EPI, body weight, age, hepatic impairment, race/ethnicity, concomitant CYP3A4 inhibitors, HbA1C levels. The following sections summarize the results of these time to event analyses.

14.3.3.2. Applicant's Time to Event Analyses

The Applicant developed time to event models to describe the relationship between finerenone concentration versus renal and cardiovascular outcomes. The renal outcome was a composite of any of the following 3 events: First occurrence of kidney failure (End-stage renal disease (ESRD) or and eGFR of $< 15\text{mL/min/1.73m}^2$; a sustained decrease of eGFR $\geq 40\%$ from baseline over at least 4 weeks; and renal death. The cardiovascular outcome was a composite of any of the following events: Cardiovascular death; non-fatal myocardial infarction; non-fatal stroke, or hospitalization for heart failure.

The models were developed using response data from the FIDELIO-DKD study and individual predicted PK parameters from the Applicant's final PopPK model. An overview of number of events used for interim and final analyses is given in Table 146.

Table 146. Overview of the Event Data in the Interim and Final Analysis Datasets

Event type	Interim Analysis		Final Analysis	
	Placebo	Active	Placebo	Active
	N,events/N,subjects (% of subjects)	N,events/N,subjects (% of subjects)	N,events/N,subjects (% of subjects)	N,events/N,subjects (% of subjects)
Renal composite	375/2832 (13.2%)	333/2827 (11.8%)	600/2841 (21.1%)	504/2833 (17.8%)
CV composite	326/2832 (11.5%)	265/2827 (9.4%)	420/2841 (14.8%)	367/2833 (13.0%)

Source: Applicant's population PKPD report (#18524 / R-13178, pages 37)

The Applicant's overall TTE model development steps are summarized in the excerpt below from the Applicant's report (Figure 41 and Figure 42).

Figure 41. Applicant's TTE Model Development Steps

2.4 Methods

The interim TTE dataset was used for model development, which was performed in a stepwise fashion as described in the Analysis plan[2] (Figure 2.4:2). The model development procedure described below was applicable for development of both models (renal TTE model and CV TTE models). First, a placebo model was developed using only data from patients in the placebo arm. Significant prognostic factors (PFs) (at baseline, except for time-varying eGFR-EPI for the CV TTE model) at the 0.05 level, based on non-parametric Cox Proportional Hazard (CPH) analysis, were concurrently included in the model after appropriate lumping. This resulted in the full PF model. The optimal parametric hazard model was selected based on the Akaike information criterion (AIC) and subsequently non-significant PFs were removed via a backward deletion (BWD) procedure using a significance level of 0.01. This resulted in the interim placebo model.

Using all the data, the ER relationship was described by an E_{max} model using individual predicted finerenone concentration-time profiles based on the *posthoc* estimates from the final PopPK model developed on data from Study 16244 (FIDELIO-DKD)[1], taking the individual dosing information into account. Next, it was investigated whether inclusion of a delay and/or Hill coefficient in the E_{max} function would further improve the fit. After inclusion of the ER relationship, PFs that were removed from the model during the BWD step were re-investigated. Lastly, the need for re-lumping was checked and the hazard model was re-evaluated resulting in the final TTE model. Renal and CV TTE models were evaluated by means of visual predictive checks (VPC) using observed dose titration, dropout and treatment discontinuation. Stratifications were performed as considered appropriate, such as stratification by exposure quartiles or PFs. In case the VPCs indicated presence of bias, an attempt was made to resolve the bias.

Source: Applicant's population PKPD report (#18524 / R-13178, pages 16)
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; ER, exposure-response; PopPK, population pharmacokinetics; TTE, time to event

Figure 42. Applicant's TTE Model Development Steps

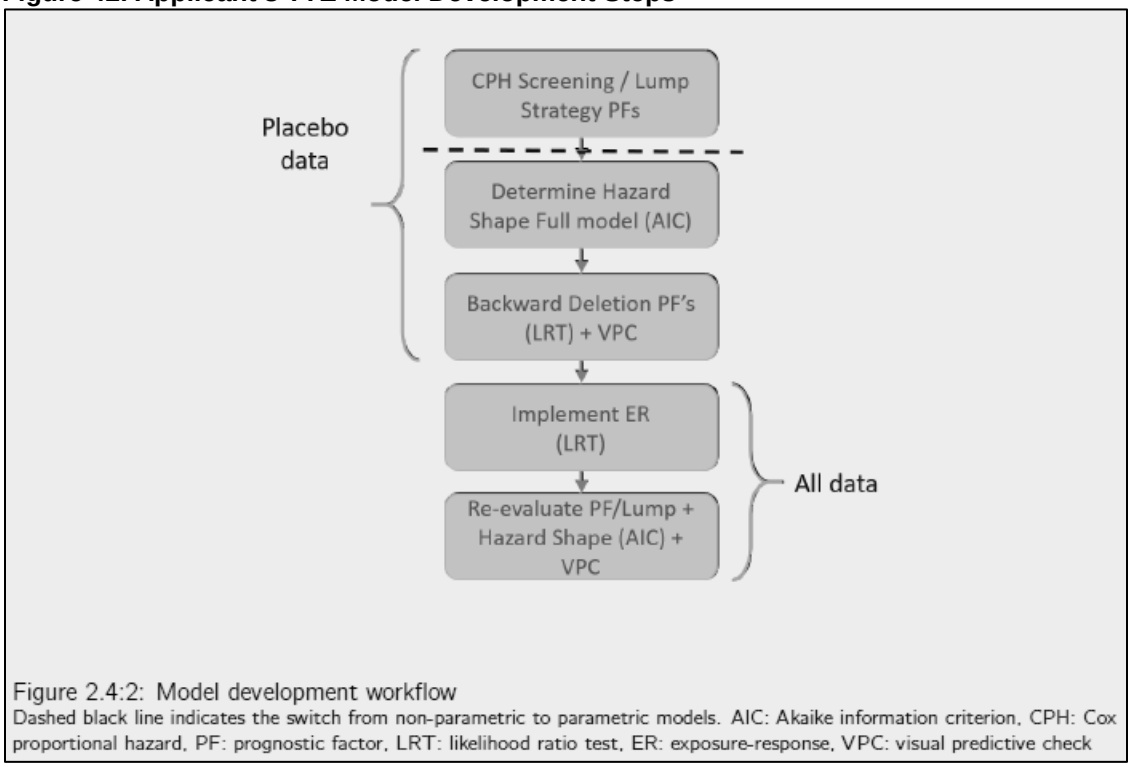


Figure 2.4:2: Model development workflow
Dashed black line indicates the switch from non-parametric to parametric models. AIC: Akaike information criterion, CPH: Cox proportional hazard, PF: prognostic factor, LRT: likelihood ratio test, ER: exposure-response, VPC: visual predictive check

Source: Applicant's population PKPD report (#18524 / R-13178, pages 17)

Finerenone Versus Primary Renal Composite Endpoint

A summary of the results of the renal TTE model building process is provided in the excerpt below, taken from the Applicant's report (Figure 43).

Figure 43. Results of the Renal TTE Model

Renal TTE model

The interim placebo TTE data for the renal composite endpoint could be described by a log-logistic hazard model. After the BWD procedure, the following PF remained in the model: Urine Albumin-to-Creatinine Ratio (UACR), eGFR-EPI at baseline (EGFREPI0), body mass index (BMI), Age, Race and likely Child Pugh Score, with UACR being the statistically most significant PF. As the visual predictive check showed that the observed KM curve of the subjects in the placebo group was contained within the 95% prediction interval, the placebo model was considered adequate to implement the ER relationship. The ER relationship was implemented as an E_{max} model with finerenone concentration in the central compartment driving the response. Inclusion of a delay or Hill coefficient in the E_{max} function was not statistically significant at the 0.05 level and was therefore discarded. Re-investigation of BWD PFs resulted in re-inclusion of SGLT-2 inhibitor use as a PF. Using that model, the log-logistic hazard model was challenged and replaced by a Weibull model, based on AIC. This resulted in the interim renal TTE model. The VPC of the interim renal TTE model, stratified by exposure quartiles (average finerenone concentration until (censored) event) indicated a slight underprediction of the event rate beyond 2 years after randomization in the first two exposure quartile groups (lowest exposure), however, it was decided to await the final data and investigate possible solutions, if still needed, based on the final data.

Using the final TTE dataset, the interim renal TTE model was rerun and parameters were re-estimated, resulting in the final renal TTE model. The VPCs, stratified by exposure quartiles (Figure 2.5:3), indicated a slight overprediction of the event rate in the first two years in the placebo group, however, the observed KM curve for each exposure quartile was generally contained within the 95% prediction interval. As expected, the event rate decreases with higher exposure. In addition, VPCs stratified by PFs in general indicated an adequate description of the data. Therefore, this model was accepted as the final model.

The maximum decrease of the hazard (E_{max}) and the EC_{50} were estimated to be 37.1% and 0.165 μg/L, respectively. Based on typical subject simulations, $C_{max,md}$ was 114 fold higher than the EC_{90} after 20 mg finerenone OD. The simulated duration above the EC_{90} within a 24h dosing interval was 16.2 h after 10 mg finerenone OD at steady-state and 19.3 h after 20 mg finerenone OD at steady-state for a typical subject.

Source: Applicant's population PKPD report (#18524 / R-13178, pages 17)
Abbreviations: AIC, Aka ke information criterion; BWD, backward deletion; eGFR, estimated glomerular filtration rate; ER, exposure-response; OD, once daily; PF, prognostic factor; PopPK, population pharmacokinetics; SGLT, sodium-glucose linked transporter; TTE, time to event; VPC, visual predictive check

The parameter estimates of the Applicant's final TTE model for the renal composite endpoint are given in Table 147. The time to events follows a Weibull distribution with lambda (λ) and alpha (α) parameters of -19.1 and 1.80 respectively. These parameters were precisely estimated with RSE <5%. The table also shows significant exposure-response relationship with precisely estimated parameters for E_{max} and EC50. The estimated maximum decrease in hazard was 37.1% and the estimated concentration to achieve half-maximum decrease was 0.165 ng/mL. The estimated EC50 was well below most of the observed finerenone plasma concentrations.

Table 147. Parameter Estimates and Uncertainties of the Final Renal Composite TTE Model

Parameter Name	Estimate	SE	RSE (%)	95% CI
Lambda (log scale, Weibull hazard)	-19.1	0.373	1.95	(-19.9 - -18.4)
Alpha (Weibull hazard)	1.80	0.0385	2.14	(1.72 - 1.87)
E_{max}	-0.371	0.0452	12.2	(-0.459 - -0.282)
EC_{50}	0.165	0.0516	31.2	(0.0643 - 0.267)
HILL	1 FIX	-	-	-
Age (log-transformed)	-1.08	0.202	18.8	(-1.47 - -0.680)
Body mass index (log-transformed)	-0.870	0.173	19.9	(-1.21 - -0.531)
eGFR-EPI at baseline (log-transformed)	-0.566	0.114	20.2	(-0.790 - -0.342)
UACR (log-transformed)	1.05	0.0470	4.46	(0.962 - 1.15)
Likely / certain Child-Pugh B	0.768	0.170	22.2	(0.434 - 1.10)
SGLT-2 inhibitor use >0-100%	-0.282	0.0835	29.6	(-0.445 - -0.118)
Black/African-American	1.02	0.246	24.2	(0.534 - 1.50)
All Asian ethnicities except Japanese	0.213	0.0926	43.5	(0.0315 - 0.394)

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI;

Source: Applicant's population PKPD report (#18524 / R-13178, pages 40)
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; RSE, relative standard error; SE, standard error, SGLT, sodium-glucose linked transporter; TTE, time to event; UACR, urine-a bumin-creatinine ratio

Table 147 shows the visual predictive check of the final renal TTE model. A slight overprediction of renal events can be observed in the placebo group during the first 2 years. However, the observed Kaplan Meier curves for the finerenone exposure quartiles are generally contained within the 95% prediction interval (Figure 44).

Figure 44. Visual Predictive Check of the Applicant's Final Renal TTE Model

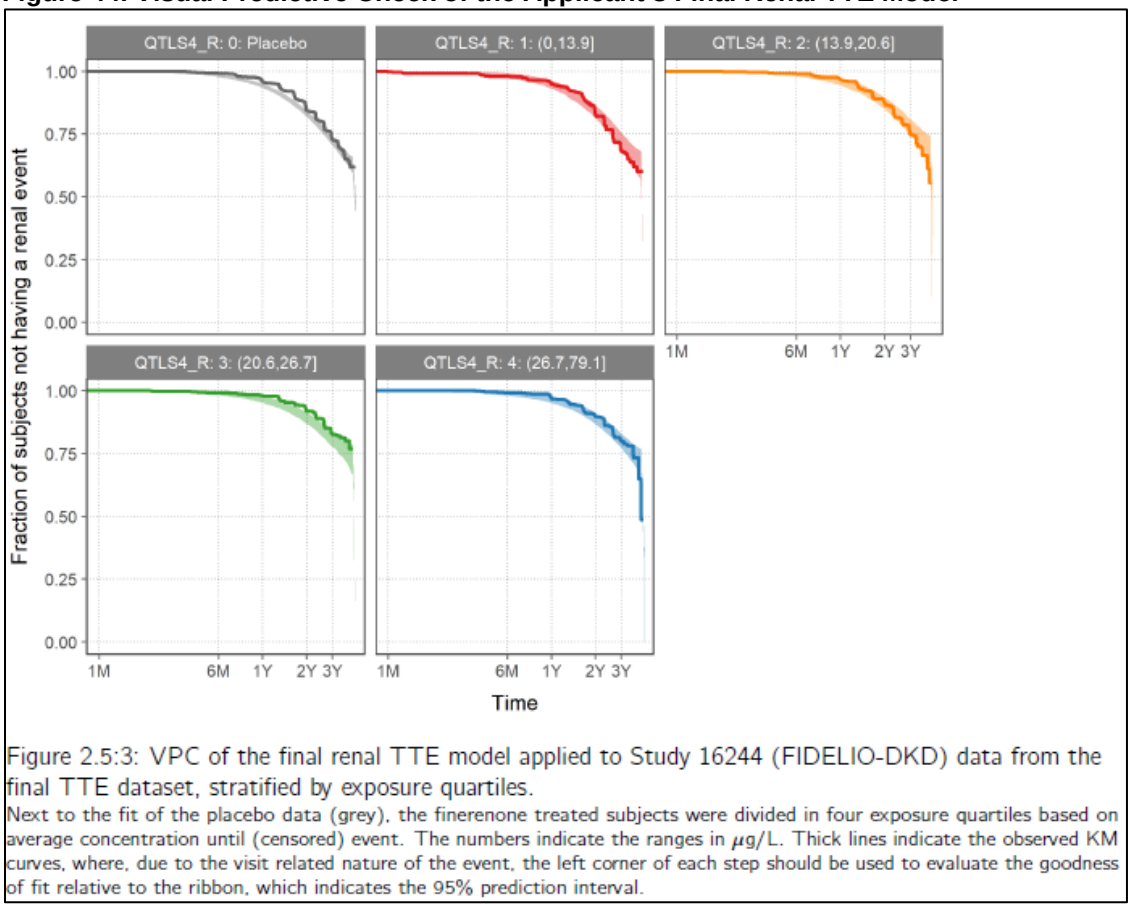


Figure 2.5:3: VPC of the final renal TTE model applied to Study 16244 (FIDELIO-DKD) data from the final TTE dataset, stratified by exposure quartiles.

Next to the fit of the placebo data (grey), the finerenone treated subjects were divided in four exposure quartiles based on average concentration until (censored) event. The numbers indicate the ranges in μg/L. Thick lines indicate the observed KM curves, where, due to the visit related nature of the event, the left corner of each step should be used to evaluate the goodness of fit relative to the ribbon, which indicates the 95% prediction interval.

Source: Applicant's population PKPD report (#18524 / R-13178, pages 18)
Abbreviations: KM, Kaplan-Meier; TTE = time to event; VPC, visual predictive check

An overview of the impact of the covariates on the hazards of renal events is given in Table 148. Covariates with high impact on hazards of events were UACR at baseline and race/ethnicity.

Table 148. Overview of the Impact of the Prognostic Factors in the Final Renal TTE Model

Table 2.5:2: Overview of PFs for final renal TTE model

Prognostic factor	Effect
UACR at baseline (UACR0)	85.0% decrease - 323% increase of the hazard at the 5^{th}-95^{th} percentiles of UACR distribution (140-3366 mg/g)
eGFR-EPI at baseline (EGFREPI0)	31.0% increase - 21.1% decrease of the hazard at the 5^{th}-95^{th} percentiles of eGFR-EPI distribution (26.7-66.9 ml/min/1.73m^2)
Body mass index at baseline (BMI0)	28.4% increase - 24.5% decrease of the hazard at the 5^{th}-95^{th} percentiles of BMI distribution (22.8-42.0 kg/m^2)
Age at baseline (AGE)	35.0% increase - 17.6% decrease of the hazard at the 5^{th}-95^{th} percentiles of Age distribution (50-79 years)
Race/Ethnicity (RACEASIA)	Black/African American: 102% increase of the hazard *versus* all other ethnicities/races
	All Asian ethnicities, except Japanese: 21.3% increase of the hazard *versus* all other ethnicities/races
SGLT-2 inhibitor use (GLYCSICN)	SGLT-2 inhibitor use for more than 0% of the at-risk period (>0-50% and >50% use combined): 28.2% decrease of the hazard *versus* no SGLT-2 inhibitor use during the at-risk period
Likely Child-Pugh Score (CHILDPSC)	Likely or certain Child-Pugh B: 76.8% increase of the hazard *versus* likely Child-Pugh A

Source: Applicant's population PKPD report (#18524 / R-13178, pages 19)
Abbreviations: eGFR, estimated glomerular filtration rate; PF, prognostic factors; SGLT, sodium-glucose linked transporter; TTE, time to event; UACR, urine-albumin-creatinine ratio

Finerenone Versus Primary Cardiovascular Composite Endpoint

A summary of the results of the cardiovascular TTE model building process is provided in the excerpt below, taken from the Applicant's report (Figure 45).

Figure 45. Results of the Cardiovascular TTE Model

CV TTE model

The interim placebo TTE data for the CV composite endpoint could be described by an exponential hazard model. After the BWD procedure, the following PF remained in the model: Age, UACR, body weight (WGHT0), time-varying eGFR-EPI (EGFREPI), HBA1C (HBA1C0) and CYP3A4 inhibitor use (CYPINHN), with Age being the statistically most significant PF. As the visual predictive check showed that the observed KM curve of subjects in the placebo group was contained within the 95% prediction interval, the placebo model was considered adequate to include the ER relationship. The ER relationship was implemented as an E_{max} model with finerenone concentration in an effect compartment driving the response, indicating a small delay between changes in concentration and the effect on the hazard. Inclusion of a Hill coefficient in the E_{max} function was not statistically significant at the 0.05 level and was therefore discarded. Re-investigation of BWD PFs resulted in re-inclusion of Race and Child-Pugh score as PFs. Using that model, the exponential hazard model was challenged, however, based on AIC the exponential model remained preferred and was therefore retained. This resulted in the interim CV TTE model. The VPC of the interim CV TTE model, stratified by exposure quartiles (average finerenone concentration until (censored) event) indicated presence of some bias in the ER relationship as the observed placebo KM curve was generally at the upper end of the 95% prediction interval, whereas the observed KM curve for active treatment data was generally at the lower end of the 95% prediction interval. It was decided to await the final data and investigate possible solutions, if still needed, based on the final data.

Using the final TTE dataset, the interim CV TTE model was rerun and parameters were re-estimated, resulting in the final CV TTE model. The VPCs, stratified by exposure quartiles (Figure 2.5:3), indicated that the ER relationship was reasonably well captured with generally lower event rates at higher exposure. However, in general, the observed KM curves of the subjects in the placebo group and with exposures in the lowest exposure quartile were close to the upper end of the 95% prediction interval, whereas the observed KM curves of subjects with exposures in the three highest exposure quartiles were, beyond one year after randomization, close to the lower end of the 95% prediction interval. This indicates that the treatment effect is overestimated to some extent.

Since the remaining bias is possibly caused by a small subgroup (8% of total) of patients (an unexpected higher initial event rate was observed in the KM curves for subjects with high eGFR-EPI at screening (≥ 60 ml/min/1.73m^2) compared to subjects with low eGFR-EPI at screening (< 60 ml/min/1.73m^2)), the CV model was accepted as final model.EC_{50} was estimated to be 12.9 μg/L (effect compartment concentration). The maximum effect (E_{max}) was fixed to 100% decrease of the hazard. Based on typical subject simulations, the EC_{90} was not reached ($C_{max,md}$ in the effect compartment was 22% below the EC_{90} after 20 mg finerenone OD). Table 2.5:2 summarizes the influence of PFs on the hazard for the final CV TTE model.

Source: Applicant's population PKPD report (#18524 / R-13178, pages 19-20)
Abbreviations: AIC, Aka ke information criterion; BWD, backward deletion; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ER, exposure-response KM, Kaplan-Meier; PF, prognostic factors; TTE, time to event; UACR, urine-albumin-creatinine ratio; VPC, visual predictive check

Figure 46 shows the visual predictive check of the final cardiovascular TTE model. The observed Kaplan Meier curves for the finerenone exposure quartiles are generally contained within the 95% prediction interval, although at the upper-end or lower-end of the interval for some quartiles.

Figure 46. Visual Predictive Check of the Final CV Composite TTE Model

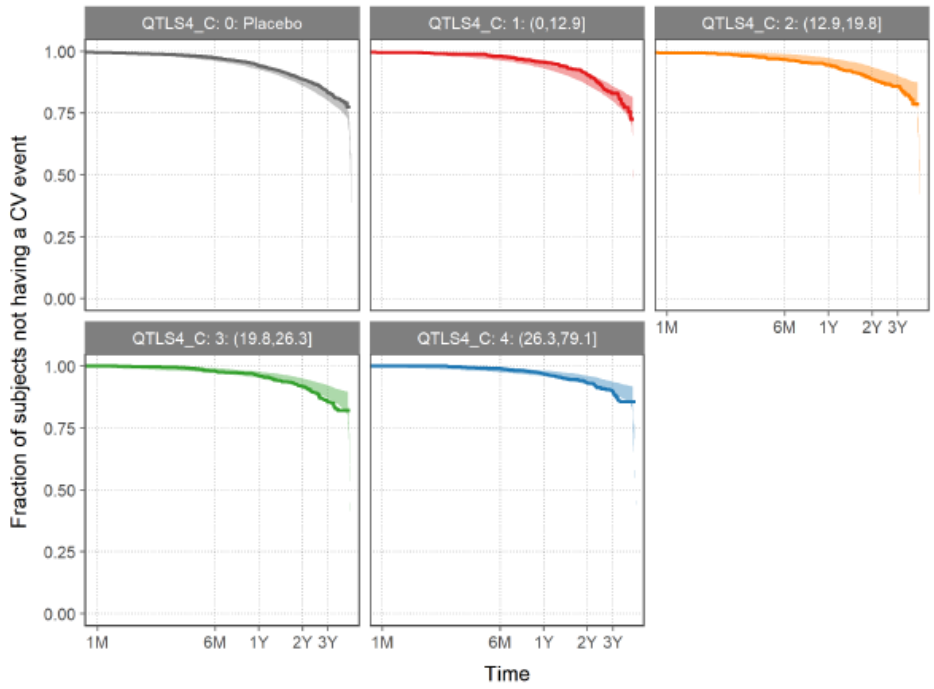


Figure 2.5:4: VPC of the final CV TTE model applied to Study 16244 (FIDELIO-DKD) data from the final TTE dataset, stratified by exposure quartiles.
Next to the fit of the placebo data (grey), the finerenone treated subjects were divided in four exposure quartiles based on average concentration until (censored) event. The numbers indicate the ranges in μg/L. Thick lines indicate the observed KM curves and the ribbons indicate the 95% prediction intervals.

Source: Applicant's population PKPD report (#18524 / R-13178, pages 20)
Abbreviations: CV, cardiovascular; KM, Kaplan-Meier; TTE = time to event; VPC, visual predictive check

An overview of the impact of the covariates on the hazards of cardiovascular events is given in Table 149. Covariates with high impact on hazards of events were age, race/ethnicity and CYP3A4 inhibitor use.

Table 149. Overview of the Impact of the Prognostic Factors in the Final CV TTE Model

Table 2.5:3: Overview of PFs for final CV TTE model

Prognostic factor	Effect
Age at baseline (AGE)	41.3% decrease - 54.2% increase of the hazard at the 5^{th}-95^{th} percentiles of Age distribution (50-79 years)
UACR at baseline (UACR0)	27.6% decrease - 27.9% increase of the hazard at the 5^{th}-95^{th} percentiles of UACR distribution (140-3366 mg/g)
Body weight at baseline (WGHT0)	16.8% decrease - 19.7% increase of the hazard at the 5^{th}-95^{th} percentiles of BMI distribution (58.6-123 kg)
eGFR-EPI, time varying (EGFREPI)	19.5% increase - 15.2% decrease of the hazard at the 5^{th}-95^{th} percentiles of eGFR-EPI distribution at baseline (26.7-66.9 ml/min/1.73m^2)
HbA1c at baseline (HBA1C0)	18.9% decrease - 41.1% increase of the hazard at the 5^{th}-95^{th} percentiles of HbA1c distribution at baseline (5.80-10.3%)
Likely Child-Pugh Score (CHILDPSC)	Likely or certain Child-Pugh B: 57.8% increase of the hazard *versus* likely Child-Pugh A
Race/Ethnicity (RACEASIA)	East Asia (Japanese + Korean + Chinese): 39.7% decrease of the hazard, all other races/ethnicities, except White: 12.7% decrease of the hazard *versus* White
CYP3A4 inhibitor use (CYPINHN)	Weak CYP inhibitor use for >0-50% of the at-risk period: 106% increase of the hazard *versus* no CYP3A4 inhibitor use Weak CYP inhibitor use for >50% of the at-risk period: 38.5% increase of the hazard *versus* no CYP3A4 inhibitor use Moderate, Strong and Unclassified CYP3A4 inhibitor use >0% of the at-risk period combined: 63.8% increase of the hazard *versus* no CYP3A4 inhibitor use

Source: Applicant's population PKPD report (#18524 / R-13178, pages 21)
Abbreviations: BMI, body mass index; CV, cardiovascular; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; TTE = time to event; UACR, urine-albumin-creatinine ratio

The parameter estimates of the Applicant's final cardiovascular TTE model are given in Table 153. The time to events follows an exponential distribution model with lambda (λ) parameters of -12.1. The maximum decrease in hazard was fixed to 100% and the estimated concentration to achieve half-maximum decrease was 12.9 ng/mL.

Table 150. Parameter Estimates and Uncertainties of the Final CV Composite TTE Model

Parameter Name	Estimate	SE	RSE (%)	95% CI
Lambda (log scale, Exponential hazard)	-12.1	0.0932	0.768	(-12.3 - -12.0)
E_{max}	-1 FIX	-	-	-
EC_{50}	12.9	2.68	20.7	(7.68 - 18.2)
HILL	1 FIX	-	-	-
Delay rate	0.509	0.100	19.8	(0.312 - 0.705)
Age	0.0333	0.00456	13.7	(0.0244 - 0.0422)
eGFR-EPI time-varying (log-transformed)	-0.373	0.0881	23.6	(-0.546 - -0.200)
HbA1c	0.123	0.0272	22.2	(0.0695 - 0.176)
UACR (log-transformed)	0.179	0.0402	22.4	(0.101 - 0.258)
Body weight (log-transformed)	0.491	0.188	38.3	(0.123 - 0.860)
Likely / certain Child-Pugh B	0.578	0.209	36.2	(0.168 - 0.988)
Weak CYP3A4 inhibitor use <50% of at-risk period	1.06	0.263	24.7	(0.548 - 1.58)
Weak CYP3A4 inhibitor use >50% of at-risk period	0.385	0.138	35.8	(0.115 - 0.654)
Moderate, Strong and Unclassified CYP3A4 inhibitor use >0% of at-risk period	0.638	0.208	32.7	(0.229 - 1.05)
East Asian (Chinese+Japanese+Korean)	-0.397	0.0706	17.8	(-0.536 - -0.259)
All other Races/Ethnicities, except White	-0.127	0.0935	73.6	(-0.310 - 0.0562)

RSE (%) is calculated as SE/Estimate*100; 95% CI is calculated as Estimate +/- 1.96*SE; for back-transformed parameters 95% CI is back-transformed values of 95% CI;

Source: Applicant's population PKPD report (#18524 / R-13178, pages 47)
Abbreviations: CI, confidence interval; CV, cardiovascular; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; RSE, relative standard error; SE, standard error; TTE = time to event; UACR, urine-albumin-creatinine ratio

Reviewer's Comment

The Applicant's analyses are acceptable for drawing conclusions about exposure-response relationships for renal and cardiovascular composite events at the recommended finerenone dosing. Despite the slight overprediction or underprediction of the events, the model is in large part able to characterize the distribution of the time to the events. The modeling process followed acceptable pharmaco-statistical principles. The reviewer repeated the Applicant's analyses and obtained results that were similar to the Applicant's.

14.4. PBPK Review

Executive Summary

The objective of this review is to evaluate the adequacy of the following Applicant PBPK reports to support the intended uses.

BAY94-8862/20189/PH-40288: Exploratory analysis of the pharmacokinetics of finerenone using physiologically based pharmacokinetic (PBPK) modeling.

- BAY94-8862/20923/PH-41349: Exploratory physiologically based pharmacokinetic (PBPK) modelling study to predict the pharmacokinetics and extent of interaction of

finerenone as victim in combination with various CYP3A4 perpetrator substances in healthy volunteers.

The Division of Pharmacometrics has reviewed the PBPK reports, supporting modeling files, and the Applicant's responses to the FDA's information requests (IRs) submitted on January 28 and March 17, 2021, and concluded the following:

- The finerenone model is adequate to predict the finerenone PK profiles following a single 1 hour intravenous infusion (0.25, 0.5 or 1 mg), a single oral dose administration (1.25, 2.5, 5, 7.5 or 10 mg), or multiple oral dose administration (10 mg BID, 20 mg BID, and 40 mg QD) in healthy subjects.
- The finerenone model is adequate to predict the effect of itraconazole or clarithromycin on finerenone PK following a single oral dose administration of finerenone (10 mg) and multiple dose administration of itraconazole (200 mg BID) or clarithromycin (500 mg BID) in healthy subjects. Model predicted finerenone geometric mean AUC ratio was higher than 5 and 3.5, when co-administered with itraconazole and clarithromycin, respectively, in healthy subjects.
- The finerenone model is adequate to predict the effect of fluvoxamine on finerenone PK following a single oral dose administration of finerenone (10 mg) and multiple dose administration of fluvoxamine (100 mg BID) in healthy subjects. Model predicted finerenone geometric mean AUC ratio was approximately 1.55 when co-administered with fluvoxamine in healthy subjects.
- The finerenone model is adequate to predict the effect of efavirenz on finerenone PK following a single oral dose administration of finerenone (10 mg) and a single dose or multiple dose administration of efavirenz in healthy subjects. Model predicted finerenone geometric mean AUC ratio was approximately 0.2, 0.2, and 0.6, when co-administered with 400 mg QD, 600 mg QD or 400 mg single dose of efavirenz, respectively, in healthy subjects.
- The finerenone model is adequate to predict the effect of rifampicin on finerenone PK following a single oral dose administration of finerenone (10 mg) and multiple dose administration of rifampicin (600 mg QD) in healthy subjects. Model predicted finerenone geometric mean AUC ratio was approximately 0.07 when co-administered with rifampicin in healthy subjects.
- Model extrapolation of clinical study results with moderate inhibitors to the studies with strong modulators may result in uncertainties regarding the predicted exposure change with strong modulators.

Applicant's PBPK Modeling Effort

PBPK Software

PK-Sim V7.4 and 9.1 (Open Systems Pharmacology) was used by the Applicant to develop the PBPK models and DDI predictions. The reviewer used the PK-Sim V 9.1 for analyses.

Model Development

Finerenone

Finerenone is available as a film-coated tablet. Its pKa is 4.30 and exhibits a typical weak base pH-dependent solubility. The solubility decreases with the increase in pH with a low solubility of 0.024 mg/mL at pH 6.8. Weibull cumulative distribution functions were fitted to the clinical observed PK data to obtain the dissolution parameters "dissolution time ((b) (4) % dissolved" and the "dissolution shape" of the tablet formulations for 1.25, 2.5, 5, 7.5, 10, and 20 mg tablets. The apparent permeability of finerenone is high in Caco-2 cells and its absorption is rapid after oral administration with a range of t_{max} of 0.5 to 1.25 h under fasting condition. Complete absorption after oral administration was indicated in human as evidenced by the complete recovery of radioactivity in the mass balance study and the very low excreted levels (<1%) of unchanged finerenone in feces and urine along with the demonstrated stability of finerenone in feces. About 19% decrease in C_{max} and 21% increase in AUC were observed in the study under fed condition compared to those under fasting condition (Study 16536). The small increase in AUC with food is likely due to the reduced first-pass clearance instead of the effect on the solubility.

The plasma protein binding (fu) for finerenone is about 8.3%. The volume of distribution of finerenone at steady state is about 52.6 to 66.9 L following iv administration. The standard PK-Sim 3-compartment model (intracellular, interstitial and vascular space) with a single permeation barrier between the interstitial and intracellular space in each organ was used to characterize the distribution of finerenone. The tissue to plasma partition coefficients of finerenone was estimated using Rodgers and Rowland's method.

Finerenone is a substrate of CYP3A4 and CYP2C8. CYP3A4 is the major enzyme involved in the oxidative biotransformation of finerenone, with an estimated fraction metabolized of 0.9 (Study PH-395340). The contribution of CYP2C8 is about 0.1 as evidenced by a ~10% increase in AUC of finerenone in a clinical study when co-administered with gemfibrozil (a strong CYP2C8 inhibitor, Study 15112). In human plasma, finerenone accounted for 7.1% of the total radioactivity, and the major metabolites M-1, M-2 and M-3 accounted for 48.9, 21.5 and 9.0% of total radioactivity, respectively (Study 14502). None of the metabolites of finerenone are pharmacologically active. Dose-proportionality increase in exposure of finerenone was observed for doses between 1.25 and 80 mg. The oral absolute bioavailability was 43.5% as determined from a 5 mg IR tablet and an IV dose of 1 mg (Study 16535). The fraction escaping gut wall elimination (FG) and hepatic elimination (FH) were estimated to be 0.575 and 0.756, respectively (Study 16535).

In the mass balance study, about 79.6% and 21.2% of the administered dose of finerenone were recovered in urine and feces, respectively (Study 14502). Unchanged finerenone in feces and urine were less than 1% of the administered dose. In addition, finerenone was shown to be stable in human feces. Renally clearance of finerenone ranged from 0.35 to 0.389 L/h across different in vivo studies, which are similar to the calculated age-normalized fu* GFR values, indicating that finerenone was eliminated via GFR only. The total clearance of finerenone was 22.3 to 31.4 L/h after iv administration. The terminal half-lives in the dose range up to 20 mg were within 2 to 3 hours.

In vitro study showed that finerenone was a substrate of P-gp (Study 40755), but not of BCRP (Study 40764). The PK properties of finerenone observed in in vitro and in vivo clinical studies, such as the high permeability, complete absorption after oral administration and no active

secretion clearance involved in the renal excretion, indicate no clinical relevance of P-gp mediated transport in vivo.

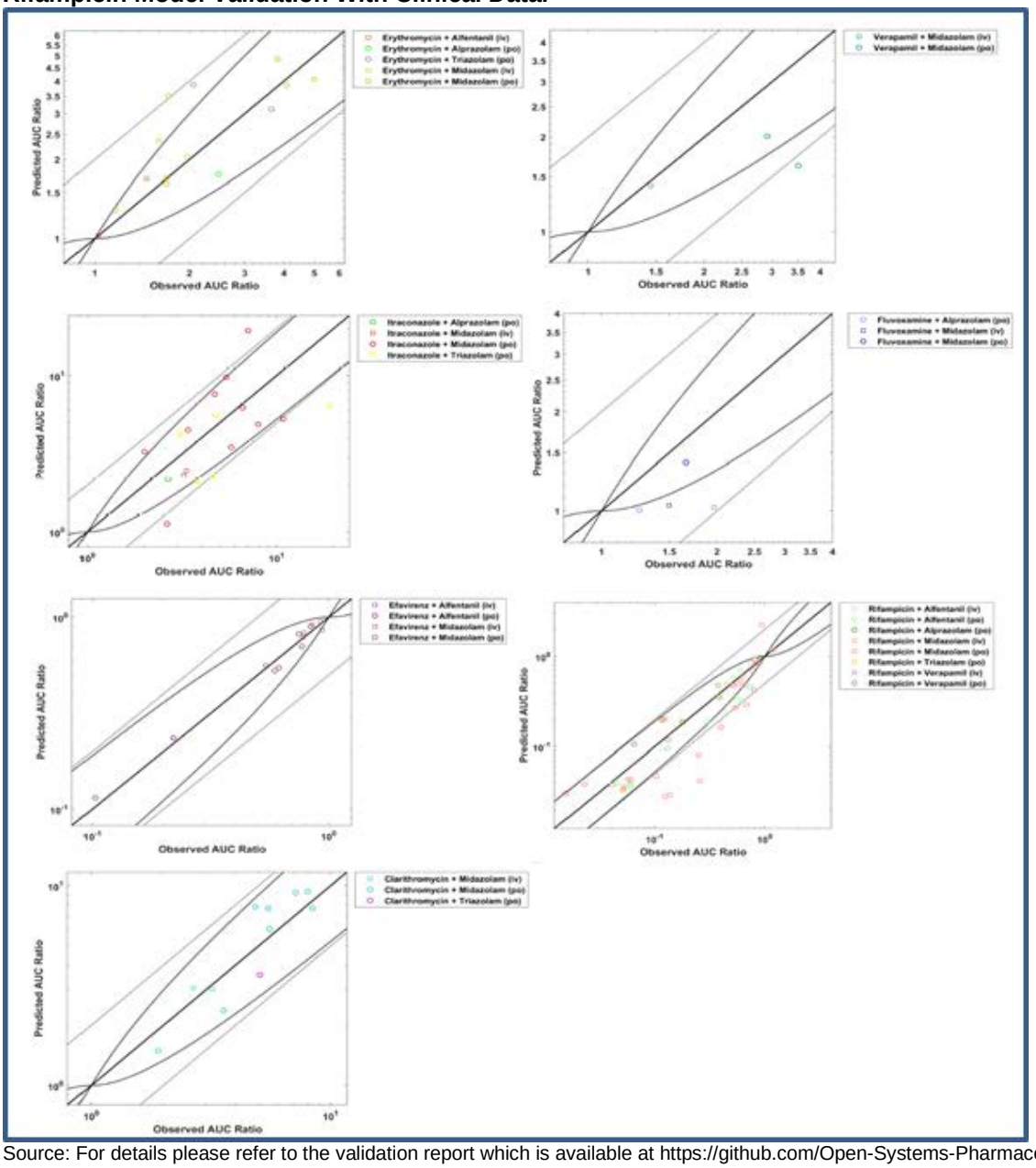
In vitro study results (Study PH-37733) along with the in vivo finerenone exposure (Study 13785) suggested finerenone has the potential to be an inhibitor of CYP3A4 in vivo, with both competitive inhibition (IC50=12 μM) and time-dependent inhibition (KI =10 μM and kinact =0.012 /min).

Perpetrator Drug Models

Erythromycin, Verapamil, Itraconazole, Clarithromycin, Fluvoxamine, Efavirenz and Rifampicin

Erythromycin, verapamil, itraconazole, clarithromycin and fluvoxamine are CYP3A inhibitors. Efavirenz and rifampicin are CYP3A inducers. The PBPK models of these inhibitors and inducers were developed in PK-Sim to evaluate the DDI potential of finerenone as a CYP3A substrate. The developed PBPK models and evaluation reports are available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library). These inhibitors/inducers-mediated inhibition/induction effect on CYP3A pathway was validated with clinical DDI studies with multiple CYP3A substrates. The DDI evaluation reports are available on the Open System Pharmacology website (https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/tree/v9.1.1/DDI_Qualification_CYP3A4). Representative DDI validation results are shown in Figure 47.

Figure 47. Erythromycin, Verapamil, Itraconazole, Clarithromycin, Fluvoxamine, Efavirenz, and Rifampicin Model Validation With Clinical Data.



Source: For details please refer to the validation report which is available at https://github.com/Open-Systems-Pharmacology/OSP-Qualification-Reports/tree/v9.1.1/DDI_Qualification_CYP3A4

FDA's Assessment

This is a PBPK analysis where a finerenone PBPK model was verified using clinical DDI study results with moderate CYP3A4 inhibitors and the model was used to evaluate the DDI potential of finerenone with strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers. Finerenone is a substrate of CYP3A4 and CYP2C8. The estimated fractions metabolized by CYP3A4 and CYP2C8 were 0.9 and 0.1, respectively, based on in vitro phenotyping studies (Study PH-395340) and clinical DDI studies with moderate CYP3A4 inhibitors (erythromycin Study 14504 and verapamil Study 16910). The fm values obtained from DDI studies with moderate inhibitors may result in uncertainties regarding the predicted exposure change with strong modulators,

especially for drugs having a high fm value. In PBPK modeling practice, clinical data with strong modulators are usually used to anchor the PBPK model performance by accurately estimating fraction metabolized by a particular enzyme. An information request was issued requesting the Applicant to evaluate the uncertainty regarding the DDI potential of finerenone with strong CYP3A4 inhibitors, moderate or strong CYP3A4 inducers.

Applicant's Response to FDA's IR and FDA's Assessment

In the response to the FDA's IR, the Applicant has explored various fmCYP3A4 values for finerenone based on current available information to reduce the uncertainty regarding the extrapolation of clinical study results with moderate CYP3A4 inhibitors to the studies with strong CYP3A4 modulators. As shown in Table 151, all model predicted AUC changes were close to the observed AUC change with moderate CYP3A4 inhibitors (Study 14504, 16910).With a fmCYP3A4 of 0.85, the predicted AUCR with verapamil is the closest to the observed AUCR. With a fmCYP3A of 0.90, the predicted AUCR values with erythromycin were the closest to the observed AUCRs. Of note, the verapamil perpetrator model was only validated against three DDI studies with midazolam, while erythromycin model was validated against multiple DDI studies with various CYP3A substrate (Figure 47). Table 151 also showed that the AUC fold change with strong modulators is more sensitive to the fm values comparing to moderate modulators.

Table 151. fmCYP3A4 and fmCYP2C8 Values and Simulated AUCR and AUC Fold-Change of Finerenone When Co-Administered With CYP3A4 Inhibitors or Inducers

	fmCYP3A4=0.85 fmCYP2C8=0.15		fmCYP3A4=0.90 fmCYP2C8=0.10		fmCYP3A4=0.95 fmCYP2C8=0.05		Observed	
	AUCR	AUC fold-change	AUCR	AUC fold-change	AUCR	AUC fold-change	AUCR	AUC fold-change
Erythromycin 500 mg, TID	3.19		3.46		3.74		3.48[b]	
Verapamil 120 mg on day 1 and followed by 240 mg daily	2.73		2.91		3.09		2.70[c]	
Gemfibrozil[a] 600 mg, BID	1.19		1.11		1.06		1.10[d]	
Itraconazole 200 mg, BID	5.18		6.33		7.86			
Clarithromycin 500 mg, BID	3.55		4.07		4.63			
Fluvoxamine 100 mg, BID	1.52		1.55		1.57			
Efavirenz 600 mg, QD	0.20	*5.0*	0.19	*5.26*	0.18	*5.56*		
Efavirenz 400 mg, QD	0.21	*4.76*	0.20	*5.0*	0.20	*5.0*		
Efavirenz 400 mg, single dose	0.60	*1.67*	0.58	*1.72*	0.57	*1.75*		
Rifampicin 600 mg, QD	0.072	*13.8*	0.069	*14.5*	0.066	*15.2*		

Source: b: Study 14504; c: Study 16910; d: Study 15112
a: the gemfibrozil mediated-CYP2C8 inhibitory effect was modelled statically assuming complete inhibition of the CYP2C8 pathway.
Abbreviations: AUC, area under the curve; AUCR, area under the curve ratio; BID, twice daily; CYP, cytochrome P450; QD, once daily

PBPK Model Application

The developed PBPK model was used to simulate the DDI for finerenone in the following scenarios.

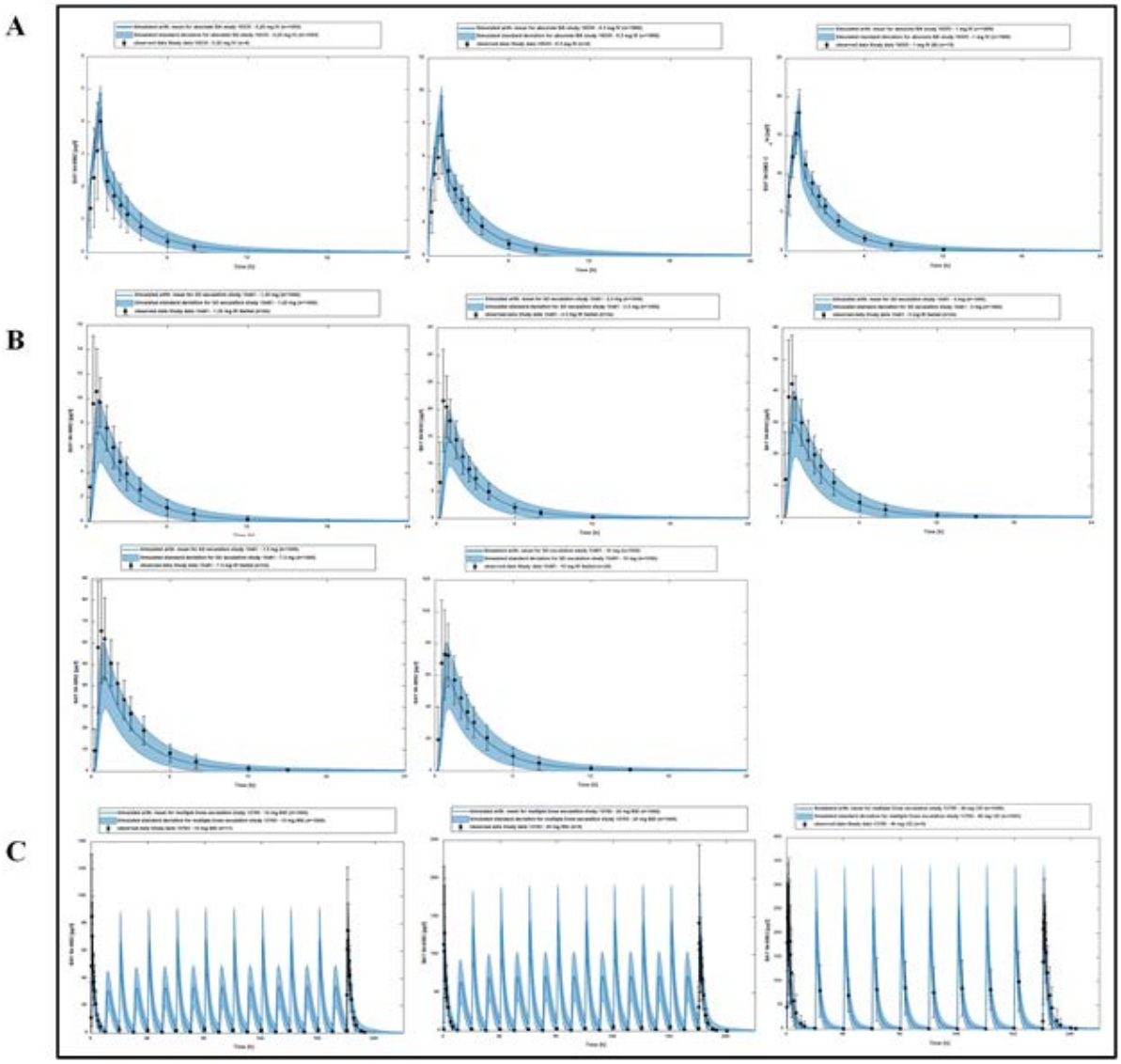
- To predict the effect of itraconazole and clarithromycin (strong CYP3A inhibitors) and fluvoxamine (a moderate to weak CYP3A inhibitor) on the PK of finerenone following administration in healthy subjects.
- To predict the effect of rifampicin (a strong CYP3A inducer) and efavirenz (a moderate CYP3A inducer) on the PK of finerenone following administration in healthy subjects.

Results

- Can finerenone PBPK model describe finerenone PK in healthy subjects?

Yes. The finerenone model was able to capture the observed finerenone PK profiles following a single 1 hour intravenous infusion (0.25, 0.5 or 1 mg, Study 16535), a single oral dose administration (1.25, 2.5, 5, 7.5 or 10 mg, Study 15481), or multiple oral dose administration (10 mg BID, 20 mg BID, or 40 mg QD, Study 13785) in healthy subjects (Figure 48 and Table 152).

Figure 48. Observed (Black Dots) and Simulated (Blue Lines) Finerenone Concentration-Time Profiles Following Administration of Finerenone in Healthy Subjects.



Source: Observed data were from study 16535 (A), study 15481 (B) and study 13785.

(A) Single 1-hour IV Infusion (0.25, 0.5, or 1 mg) (Study 16535)
(B) Single oral (1.25, 2.5, 5, 7.5, or 10 mg) (Study 15481)
(C) Multiple oral (10 mg BID, 20 mg BID or 40 mg BID) (Study 13785)
Abbreviations: BID, twice daily; IV, intravenous

Table 152. Observed and Simulated Finerenone Geometric Mean C_{max} and AUC and C_{max} and AUC Ratios Following a Single (IV Infusion or Oral) or Multiple Oral Dose Administration of Finerenone

Dose, route	AUC (µg*h/L) Observed/Predicted/$R_{Pred/Obs}$	C_{max} (µg/L) Observed/Predicted/$R_{Pred/Obs}$	Study #
0.25 mg, IV, SD	7.95/10.42/1.31	3.95/4.40/1.11	16535
0.5 mg, IV, SD	19.3/20.85/1.08	7.05/8.80/1.25	
1 mg, IV, SD	44.8/41.7/0.93	17.7/17.6/0.99	
1.25 mg, Oral, SD	28.4/21.74/0.77	11.8/7.20/0.61	15481
2.5 mg, Oral, SD	55.6/43.7/0.79	23.9/14.4/0.60	
5 mg, Oral, SD	118/88.2/0.75	45.6/28.9/0.64	
7.5 mg, Oral, SD	193/133/0.69	72.1/43.6/0.60	
10 mg, Oral, SD	216/179/0.83	82.3/58.3/0.71	
10 mg, Oral, BID, day 1	208/177/0.85	91/58/0.64	13785
10 mg, Oral, BID, day 10	232/198/0.85	95/68/0.72	
20 mg, Oral, BID, day 1	319/356/1.13	177/117/0.66	
20 mg, Oral, BID, day 10	420/426/1.01	171/143/0.84	
40 mg, Oral, BID, day 1	928/742/0.80	287/237/0.83	
40 mg, Oral, BID, day 10	1022/826/0.81	259/256/0.99	

Source: Indicated Studies
Abbreviations: AUC, area under the curve; BID, twice daily; IV, intravenous; SD, single dose

- Can finerenone PBPK model predict the effect of itraconazole and clarithromycin (strong CYP3A4 inhibitors) on the PK of finerenone?

Yes. The finerenone model was able to predict the effect of itraconazole or clarithromycin on finerenone PK following a single oral dose administration of finerenone and multiple dose administration of itraconazole or clarithromycin in healthy subjects. The model predicted finerenone AUCR was approximately higher than 5 or 3.55 when co-administered with itraconazole or clarithromycin in healthy subjects (Table 151), respectively. Refer to "Applicant's response to FDA's IR" for details.

- Can finerenone PBPK model predict the effect of fluvoxamine (a moderate CYP3A4 inhibitor) on the PK of finerenone?

Yes. The finerenone model validated using clinical data with moderate CYP3A inhibitors was adequate to predict the effect of fluvoxamine on the PK of finerenone following a single oral dose administration of finerenone and multiple dose administration of fluvoxamine in healthy subjects. The model predicted finerenone AUCR was approximately 1.55 when co-administered with fluvoxamine in healthy subjects Table 151. Refer to "Applicant's response to FDA's IR" for details.

- Can finerenone PBPK model predict the effect of efavirenz (a moderate CYP3A4 inducer) on the PK of finerenone?

Yes. The finerenone model validated using clinical data with moderate CYP3A inhibitors was adequate to predict the effect of efavirenz on finerenone PK following a single oral dose administration of finerenone and a single or multiple dose administration of efavirenz in healthy subjects. The model predicted finerenone AUCR was approximately 0.2, 0.2, or 0.6, respectively,

when co-administered with efavirenz (400 mg QD, 600 mg QD or 400 mg single dose) in healthy subjects (Table 151). Refer to "Applicant's response to FDA's IR" for details.

- Can finerenone PBPK model predict the effect of rifampicin (a strong CYP3A4 inducer) on the PK of finerenone?

Yes. The finerenone model was able to predict the effect of rifampicin on finerenone PK following a single oral dose administration of finerenone and multiple dose administration of rifampicin in healthy subjects. The model predicted finerenone AUCR was approximately 0.07 when co-administered with rifampicin in healthy subjects (Table 151). Refer to "Applicant's response to FDA's IR" for details.

14.5. Summary of Bioanalytical Method Validation and Performance

Bioanalytical methods were reviewed for both finerenone and the metabolites M-1 (BAY 1040818), M-2, (BAY 088089), and M-3 (BAY 1088090). Bioanalytical methods are summarized below (Table 153 and Table 154).

Table 153. Plasma Bioanalytical Methods Overview

Analyte	Finerenone (BAY 94-8862)	Simultaneous Finerenone + Metabolites M-1 (BAY 1040818), M-2 (BAY 1088089), M-3 (BAY 1088090)
Method name, site, and dates in use	MW1398, Bayer AG, 08/2009-07/2016 MW1921, Bayer AG, 01/2017-02/2018 MW2007, Bayer AG, 10/2017-11/2017 (b) (4)-13062, (b) (4), in use since 10/2013	MW1452, Bayer AG, 09/2010-11/2014 (b) (4)-14068, (b) (4), 07/2014-11/2016 MW1452, Bayer AG, 08/2011-08/2011 (for plasma ultrafiltrate)
Precision and accuracy	Concentrations above the lower limit of quantification (LLOQ) were determined with a precision within 15% and an accuracy within 85-115%, and concentrations at the LLOQ were determined with a precision of ≤20% and accuracy within 80-120%	
Stability	In human plasma, finerenone and its metabolites were stable at ≤ −15°C for at least 22 and 12 months, respectively	

Source: Clinical pharmacology reviewer's table

Table 154. Urine Bioanalytical Methods Overview

Analyte	Finerenone (BAY 94-8862)	Simultaneous Finerenone + Metabolites M-1 (BAY 1040818), M-2 (BAY 1088089), M-3 (BAY 1088090)
Method name, site, and dates in use	MW1398, Bayer AG, 11/2009	MW1452, Bayer AG, 05/2011-11/2014 (b) (4)-14069, (b) (4) not used
Stability	Stability for at least 12 months in human urine at ≤ −20°C was proven for all analytes	

Source: Clinical pharmacology reviewer's table

Several analytical methods were used to quantify finerenone and its metabolites during the drug development period. The ones most commonly used were MW1398 and MW1452. These methods are described in more detail below; however, all methods were well described by the Applicant and reviewed (Table 155 to Table 158).

Table 155. Plasma Validation Data for Method MW1398

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142
Method	LC-MS/MS method for quantifying finerenone in human plasma
Materials for calibration curve and concentrations	Control human plasma and finerenone reference standards Calibrator concentrations: 0.100, 0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200 µg/L
Validated assay range	0.100 to 200 µg/L
Quality controls and concentration	Control human plasma and finerenone reference standards QC concentrations: 0.300, 7.00, 160 µg/L

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Regression model and weighting	Log/log, unweighted	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	11 (2 sets)
	Cumulative accuracy (%bias)	
	manual (3 batches)/automated (3 batches) at LLOQ:	-1.15%/4.96%
	manual (3 batches)/automated (3 batches) at ULOQ:	-7.96%/-0.29%
	Cumulative precision (%CV)	
	manual (3 batches)/automated (3 batches) at LLOQ	9.22%/7.02%
	manual (3 batches)/automated (3 batches) at ULOQ	2.95%/3.54%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 18 QCs (6 for each batch) manual (3 batches)/automated (3 batches):	-11.6 to -3.18%/ 2.66 to 4.16%
	Inter-batch %CV manual (3 batches)/automated (3 batches):	2.82 to 4.86%/ 3.81 to 5.39%
Selectivity	Comparing blank peak heights to the mean peak height of sample prepared at the LLOQ: ≤10.8% (analyte) and ≤0.09% (ISTD)	
Matrix Effect	Mean matrix effects (ratio of absolute peak heights/areas of matrix extract and pure standard) of analyte were sufficiently compensated by ISTD (matrix effect analyte – matrix effects ISTD within ±20%): -0.19% (0.300 µg/L), -1.19% (7.00 µg/L), and 1.66% (160 µg/L)	
Carry over	Acceptance criteria for the analyte and ISTD were ≤20% of the LLOQ signal and ≤5% of the ISTD signal (≤12.9% for the analyte and ≤0.001% for the ISTD)	

Source: Clinical pharmacology reviewer's table
Abbreviations: CV, coefficient of variation; ISTD, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 156. Plasma Validation Data for Method MW1452

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142
Method	LC-MS/MS method for quantifying finerenone, M-1, M-2, and M-3 in human plasma
Materials for calibration curve and concentrations	Control human plasma and finerenone, M-1, M-2, and M-3 reference standards Calibrator concentrations: 0.100, 0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200, 500 µg/L
Validated assay range	Finerenone: 0.100 to 500 µg/L Metabolites: 0.500 to 500 µg/L
Quality controls and concentration	Control human plasma and finerenone, M-1, M-2, and M-3 reference standards QC concentrations of about 0.300 µg/L (finerenone only), 1.56 µg/L (metabolites only), 12.5 µg/L, and 400 µg/L
Regression model and weighting	Log/log, unweighted
Validation Parameters	Method validation summary includes full (API 4000 instrument) and partial (API 5500 instrument) validation results

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators for finerenone/metabolites from LLOQ to ULOQ	12/10 (2 sets)
	Cumulative accuracy (%bias) at LLOQ	7.96%/9.01%
	Finerenone on API 4000 (3 batches)/API 5500 (1 batch):	-9.01%/2.43%
	M-1 on API 4000 (3 batches)/API 5500 (1 batch):	-4.56%/-0.01%
	M-2 on API 4000 (3 batches)/API 5500 (1 batch):	-0.72%/-1.18%
	M-3 on API 4000 (3 batches)/API 5500 (1 batch):	
	Cumulative precision (%CV) at LLOQ	18.6%/12.5%
	Finerenone on API 4000 (3 batches)/API 5500 (1 batch):	11.9%/14.8%
	M-1 on API 4000 (3 batches)/API 5500 (1 batch):	17.0%/5.97%
	M-2 on API 4000 (3 batches)/API 5500 (1 batch):	9.34%/3.30%
	M-3 on API 4000 (3 batches)/API 5500 (1 batch):	

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (% bias) in 18/6 QCs (6 for each batch):**	
	Finerenone (BAY 94-8862)	
	on API 4000 (3 batches, QCs: 0.311, 12.4, 398 µg/L) / API 5500 (1 batch, QCs: 0.310, 12.4, 400 µg/L):	-2.70 to -0.18% / -3.31% to 2.06%
	Metabolite M-1 (BAY 1040818)	
	on API 4000 (3 batches, QCs: 1.57, 12.6, 403 µg/L) / API 5500 (1 batch, QCs: 1.55, 12.4, 399 µg/L):	-3.87% to -0.49% / -3.86% to 0.52%
	Metabolite M-2 (BAY 1088089)	
	on API 4000 (3 batches, QCs: 1.57, 12.6, 402 µg/L) / API 5500 (1 batch, QCs: 1.56, 12.4, 401 µg/L):	0.14% to 1.36% / -1.61% to 4.04%
	Metabolite M-3 (BAY 1088090)	
	on API 4000 (3 batches, QCs: 1.58, 12.7, 405 µg/L) / API 5500 (1 batch, QCs: 1.55, 12.4, 400 µg/L):	-3.27% to -2.34% / -0.42% to 3.26%
	Inter-/Intra-batch %CV:	
	Finerenone (BAY 94-8862)	
	on API 4000 (3 batches, QCs: 0.311, 12.4, 398 µg/L) / API 5500 (1 batch, QCs: 0.310, 12.4, 400 µg/L):	-2.70% to -0.18% / -3.31% to 2.06%
	Metabolite M-1 (BAY 1040818)	
	on API 4000 (3 batches, QCs: 1.57, 12.6, 403 µg/L) / API 5500 (1 batch, QCs: 1.55, 12.4, 399 µg/L):	-3.87% to -0.49% / -3.86% to 0.52%
	Metabolite M-2 (BAY 1088089)	
	on API 4000 (3 batches, QCs: 1.57, 12.6, 402 µg/L) / API 5500 (1 batch, QCs: 1.56, 12.4, 401 µg/L):	0.14% to 1.36% / -1.61% to 4.04%
	Metabolite M-3 (BAY 1088090)	
	on API 4000 (3 batches, QCs: 1.58, 12.7, 405 µg/L) / API 5500 (1 batch, QCs: 1.55, 12.4, 400 µg/L):	-3.27% to -2.34% / -0.42% to 3.26%
Selectivity	Assessed by comparing blank peak heights to the mean peak height of a sample prepared at the LLOQ:	
	Finerenone	≤12.5% (analyte) ≤0.12% (ISTD)
	M-1	≤7.2% (analyte) ≤0.25% (ISTD)
	M-2	≤5.7% (analyte) ≤0.16% (ISTD)
	M-3	≤1.6% (analyte) ≤0.11% (ISTD)

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Matrix effect	Mean matrix effects (ratio of absolute peak heights/areas of matrix extract and pure standard) of analytes were sufficiently compensated by ISTD (matrix effect analyte – matrix effect ISTD within ±20%):	
	Finerenone	-0.54% (0.5 µg/L) and 0.26% (200 µg/L)
	M-1	-2.1% (0.5 µg/L) and -2.6% (200 µg/L)
	M-2	-0.04% (0.5 µg/L) and 1.9% (200 µg/L)
	M-3	3.9% (0.5 µg/L) and 2.2% (200 µg/L)
Bench-top/process stability	5 hour bench-top stability at 2.00 and 200 µg/L ISTD normalized difference (%) between 5 h and starting time point (0 h) was as follows:	
	Finerenone	2.58% (2.00 µg/L), 0.947% (200 µg/L)
	M-1	-3.58% (2.00 µg/L), -8.62% (200 µg/L)
	M-2	5.12% (2.00 µg/L), 1.32% (200 µg/L)
	M-3	0.765% (2.00 µg/L), -0.613% (200 µg/L)
Freeze-thaw stability	Low, mid, and high QC samples were prepared, stored at ≤ -15 ℃ and subjected to 3 freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV) at the respective QC level were below the following values:	
	Finerenone	
	at 0.316, 12.6, and 404 µg/L	≤±23.2, ≤±14.2, ≤±5.00 (%bias)
	M-1	≤9.63, ≤2.67, ≤3.45 (%CV)
	at 1.56, 12.5, and 399 µg/L	≤±9.39, ≤±6.79, ≤±6.34 (%bias)
	M-2	≤5.90, ≤5.69, ≤5.17 (%CV)
	at 1.56, 12.5, and 400 µg/L	≤±11.1, ≤±9.22, ≤±5.98 (%bias)
	M-3	≤6.01, ≤5.59, ≤4.06 (%CV)
	at 1.56, 12.5, and 399 µg/L	≤±3.51, ≤±2.20, ≤±7.78 (%bias)
		≤4.41, ≤8.71, ≤6.19 (%CV)
Long-term storage	Low, mid, and high QC samples were prepared, stored at ≤ -15 ℃ and subjected to 3 freeze-thaw cycles. Mean difference between nominal and observed (%bias) and precision in each batch (%CV) at the respective QC level were below the following values:	
	Finerenone at 0.300, 7.00, and 160 µg/L	660 days
	M-1 at 1.56, 12.5, and 399 µg/L	365 days
	M-2 at 1.56, 12.5, and 400 µg/L	365 days
	M-3 at 1.56, 12.5, and 399 µg/L	365 days

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Carry over	Acceptance criteria for the analyte and ISTD were ≤20% of the LLOQ signal and ≤5% of the ISTD signal:	
	Finerenone	≤7.6% (analyte) ≤0.1% (ISTD)
	M-1	≤8.6% (analyte) ≤0.2% (ISTD)
	M-2	≤9.0% (analyte) ≤2.9% (ISTD)
	M-3	≤7.1% (analyte) ≤2.0% (ISTD)

Source: Clinical pharmacology reviewer's table
Abbreviations: CV, coefficient of variation; ISTD, internal standard; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 157. Urine Validation Data for Method MW1398

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Method	LC-MS/MS method for quantifying finerenone in human urine (10-fold dilution with plasma)	
Materials for calibration curve and concentrations	Control human plasma and finerenone reference standards Calibrator concentrations in urine/plasma (1:10 mixture): 0.100, 0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200 µg/L	
Validated assay range	1.00 to 2000 µg/L (effective range for finerenone in urine) – 0.100 – 200 µg/L in urine/plasma (1:10 mixture)	
Quality controls and concentration	Control human plasma and urine, as well as finerenone standards QC concentrations in urine/plasma (1:10 mixture): 0.300, 7.00, and 160 µg/L	
Regression model and weighting	Log/log, unweighted	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	11 (2 sets)
	Cumulative accuracy (%bias) at LLOQ	0.51%
	Cumulative accuracy (%bias) at ULOQ	0.11%
	Cumulative precision (%CV) at LLOQ	7.10%
	Cumulative precision (%CV) at ULOQ	1.86%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (% bias) in 6 QCs (6 for each batch):	-3.19 to 0.83%
	Inter-/Intra-batch %CV**:**	1.00 to 5.41%
Bench-top/process stability	Not assessed – stability in urine was assessed in Method [redacted](b) (4) 14069 (Table 128)	
Freeze-thaw stability	Not assessed – stability in urine was assessed in Method [redacted] 14069 (Table 128)	
Long-term storage	Not assessed – stability in urine was assessed in Method [redacted] 14069 (Table 128)	

Source: Clinical pharmacology reviewer's table
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

Table 158. Urine Validation Data for Method MW1452

Bioanalytical Method Validation Name and Report	**Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142**	
Method	LC-MS/MS method for quantifying finerenone, M-1, M-2, and M-3 in human urine (10-fold dilution in plasma)	
Materials for calibration curve and concentrations	Control human plasma and urine as well as finerenone, M-1, M-2, and M-3 reference standards Calibrator concentrations in urine/plasma (1:10 mixture): 0.100, 0.200, 0.500, 1.00, 2.00, 5.00, 10.0, 20.0, 50.0, 100, 200, 500 µg/L	
Validated assay range	Finerenone: 1.00 - 5000 µg/L, effective range in urine: 0.100 – 500 µg/L in urine/plasma (1:10 mixture) Metabolites: 5.00 - 5000 µg/L, effective range in urine: 0.500 – 500 µg/L in urine/plasma (1:10 mixture)	
Quality controls and concentration	Control human plasma and urine, as well as finerenone, M-1, M-2, and M-3 reference standards QC concentrations in urine/plasma (1:10 mixture) of about 0.300 µg/L (finerenone only), 1.56 µg/L (metabolites only), 12.5 µg/L, and 400 µg/L	
Regression model and weighting	Log/log, unweighted	
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators for finerenone/metabolites from LLOQ to ULOQ	12/10 (2 sets)
	<u>Cumulative accuracy (%bias) at LLOQ:</u>	
	Finerenone	8.52%
	M-1	3.02%
	M-2	1.53%
	M-3	4.29%
	<u>Cumulative precision (%CV) at LLOQ</u>	
	Finerenone	8.20%
	M-1	7.58%
	M-2	4.85%
	M-3	4.33%

Bioanalytical Method Validation Name and Report	Bioanalytical Method and Validation Data for Clinical Studies Bayer Report ID: PH-41142	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (% bias) in 6 QCs (5 for each batch):** Finerenone (BAY 94-8862) 1 batch, QCs: 0.313, 12.5, and 401 µg/L Metabolite M-1 (BAY 1040818) 1 batch, QCs: 1.57, 12.5, and 401 µg/L Metabolite M-2 (BAY 1040818) 1 batch, QCs: 1.56, 12.5, and 400 µg/L Metabolite M-3 (BAY 1040818) 1 batch, QCs: 1.56, 12.5, and 400 µg/L	 -0.60 to 7.51% -1.15 to 2.18% -1.05 to 1.55% -1.12 to 3.08%
	Inter-batch %CV: Finerenone (BAY 94-8862) 1 batch, QCs: 0.313, 12.5, and 401 µg/L Metabolite M-1 (BAY 1040818) 1 batch, QCs: 1.57, 12.5, and 401 µg/L Metabolite M-2 (BAY 1040818) 1 batch, QCs: 1.56, 12.5, and 400 µg/L Metabolite M-3 (BAY 1040818) 1 batch, QCs: 1.56, 12.5, and 400 µg/L	 1.74 to 5.04% 2.26 to 4.48% 3.75 to 5.47% 3.18 to 4.19%
Dilution linearity and hook effect	~20000 µg/L (referring to urine) tested with a 50-fold dilution of urine with plasma: Finerenone M-1 M-2 M-3	 -2.50% (%bias) and 9.11% (%CV) -5.25% (%bias) and 4.60% (%CV) -0.17% (%bias) and 8.41% (%CV) 1.46% (%bias) and 5.52% (%CV)
Bench-top/process stability	Not assessed – stability in urine was assessed in Method [redacted] (b) (4) 14069 (Table 128)	
Freeze-thaw stability	Not assessed – stability in urine was assessed in Method [redacted] 14069 (Table 128)	
Long-term storage	Not assessed – stability in urine was assessed in Method [redacted] 14069 (Table 128)	

Source: Clinical pharmacology reviewer's table
Abbreviations: CV, coefficient of variation; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LLOQ, lower limit of quantification; QC, quality control; ULOQ, upper limit of quantification

15. Trial Design: Additional Information and Assessment

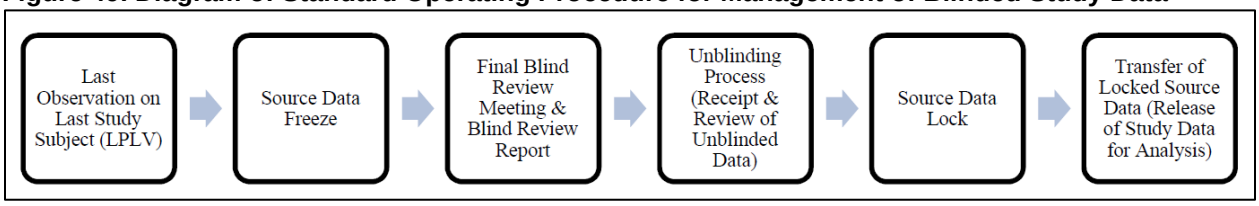
15.1. Standard Operating Procedure and Important Study Dates

The figure below shows the Applicant's standard operating procedure (SOP) for management of study data for FIDELIO-DKD and Table 159 lists the milestone events and associated dates for the FIDELIO-DKD Study. The first patient first visit occurred on September 17, 2015. The last patient last visit occurred on April 14, 2020; this was considered the "end of study" date. A "Source Data Freeze" occurred on May 22, 2020, after the Statistical Analysis Plan (SAP) was finalized. Per the sponsor, the "Source Data Freeze" includes the transfer and labelling of all final blinded data into the Data Management operating environment and can be considered an initial 'database lock' prior to unblinding." Any updates to the blinded data from that point were "transparently documented." After the final blind review meeting and the finalization of the Blind Review Report, the unblinded data became available for review to a "limited" team consisting of the study data manager, study manager, study lead monitor, study medical expert, independent unblinded statistician, and pharmacokineticist on May 25, 2020. Following the unblinded data review, a "Source Data Lock" took place on June 12, 2020, and the unblinded data were added to the blinded data. The locked source data were then transferred to a "statistical environment where statistical analysis can take place" (June 15-19, 2021).

The trial had two database locks: June 19, 2020 and July 29, 2020 because before finalization of the Clinical Study Report, "database errors were identified" after the first database lock (June 19, 2020); it "was decided to update the clinical database to correct these errors." The number of patients affected by the errors were too small to impact the conclusion of the study.

The Applicant's SOP was considered acceptable (Figure 49).

Figure 49. Diagram of Standard Operating Procedure for Management of Blinded Study Data



Source: Applicant response to FDA Request for Information dated April 15, 2021

Table 159. Key Milestone Events for the FIDELIO-DKD Study (16244)

Milestone Event/Process	Date
First Patient First Visit	September 17, 2015
Interim Analysis (database cut-off)	July 8, 2019
Interim Analysis (DMC decision)	September 25, 2019
End of Study Notification	February 3, 2020
Last Patient Last Visit	April 14, 2020
Source Data Freeze	May 22, 2020
Final Blind Review Meeting and Finalization of Blind Review Report	May 25, 2020
Unblinding Process (Receipt of Unblinded Data)	May 26, 2020
Unblinding Process (Review of Unblinded Data)	May 27-June 11, 2020
Source Data Lock	June 12, 2020
Transfer of locked source data to the Stats Programming operating environment (Release of Study Data for Analysis)	June 15-19, 2020
Unblinded data are available for statistical analysis ("Initial Data Release for Analysis") (Database Lock)	June 19, 2020
Final Data Release for Analysis (Database Lock)	July 29, 2020

Source: Applicant responses to FDA Requests for Information dated March 31, 2021 and April 15, 2021
Abbreviations: DMC, data monitoring committee

15.2. Protocol Amendments

The clinical protocol was amended globally two times. An overview of each of these amendments can be seen in Table 160.

Table 160. Overview of Integrated Protocol Amendments

Integrated Protocol Version, and Date	# of Patients Enrolled	# of Patients with Primary Endpoint Event	Summary of Significant Changes
Protocol Version 2.0 (May 2, 2017)	7264	24	Increase of anticipated study duration from 3.25 years to 4 years and site numbers from 650 to 900 to account for lower than expected recruitment rate Allowed for re-screening at an earlier stage (i.e., a minimum of 3 months between the initial Run-in visit and re-screening instead of 6 months) Modified exclusion criterion to allow randomization of patients suffering from stroke, transient ischemic attack, acute coronary syndrome or hospitalization for worsening heart failure before the last 30 days prior to the Screening visit instead of the Run-in visit Allowed for up-titration of study drug at any time during the study Updated recommended blood pressure target after randomization from <140/90 to <130/80 according to most recent literature Addition of the definition of the endpoint for "kidney failure"
Protocol Version 3.0 (Feb 26, 2019)	13911	531	Allowed for the post-treatment visit to be performed as a telephone contact Specified that baseline values should be performed *on the day of* Visit 1 prior to first dose of study drug Increased the time window for "on-treatment" analyses from 3 to 30 days after last study drug administration to better reflect the more protracted nature of the development and diagnosis of clinical outcome events of interest in relation to treatment exposure Specified the definition of TEAEs and interruptions of study treatment

15.3. Trial Administrative Structure

Clinical Event Committee

A Clinical Event Committee (CEC), which was blinded to study treatment assignment, adjudicated all events that could potentially fulfill the criteria for the primary, secondary, or other endpoints during the study (Table 163). The CEC consisted of 9 cardiologists, 6 nephrologists, and 4 neurologists who were voting members.

Potential endpoint events were each assigned to two voting members for independent review. If the initial two voting members agreed, then the event was considered adjudicated. If the initial two voting members did not agree, then the event was distributed to a third member. If the third voting member did not agree with either of the first two voting members, then the event was reviewed at a panel meeting in order to reach a decision. Panel meetings were held monthly as

needed. Cases were not discussed among CEC members, with the exception of cases to be reviewed in a panel meeting.

Data Monitoring Committee

An external and independent Data Monitoring Committee (DMC) performed ongoing safety monitoring during the conduct of the study. The DMC membership and responsibilities were defined by a written charter. The objectives of the DMC were to:

- Review aggregate and individual patient data related to safety, data integrity and overall conduct of the studies
- Review and evaluate unblinded efficacy results from a prespecified interim analysis to determine if the study should be terminated early due to overwhelming efficacy or due to futility

The committee met every six months. Each meeting began with an open session that sponsor representatives and coordinating investigators could attend. Data presented in the open session could include enrollment data, baseline characteristics, important protocol deviations, and other administrative data. This was followed by a closed session that included only individuals from the DMC and a non-voting facilitator (from an independent Statistical Analysis Center). Data which could compromise the integrity of the study (e.g., comparative data and/or any unblinded data) were analyzed and discussed only in the closed session.

The Applicant submitted minutes for meetings of the DMC. See Section 20.1 for a summary of the meeting minutes.

Executive Committee

An Executive Committee, which consisted of external experts in the area of nephrology, diabetes, and cardiology, ensured the "overarching integrity" of the study. The committee's responsibilities included: reviewing feedback from the DMC, providing input on the CEC charter, providing recommendations regarding sub-studies and amendments to the protocol, contributing to and overseeing of publications and communications of study results, projecting study termination and other study-related activities, as appropriate, and overseeing overall blinded event rates to ensure they met protocol projections.

Steering Committee

The Steering Committee consisted of country representatives and was led by the Executive Committee. The Steering Committee was blinded to study data while the trial was ongoing. The main responsibilities of the Steering Committee were to: provide input on protocol-related issues and protocol amendments that arose during the course of the study, oversee study progress and provide recommendations to the Executive Committee in regard to any necessary modifications that may be required in study conduct or study monitoring, transmission of information to individual investigators, and to serve as a resource for scientific review of sub-studies, publications, presentations, and/or educational material as applicable.

15.4. Study Assessments

Baseline Values

Baseline values were defined as the last non-missing measurement before randomization. If the last observation available prior to randomization was the measurement from the Screening visit, then this value was used as the baseline value. This also included assessments from a local laboratory, in the event that prior to randomization, no assessment from the central laboratory was available. Otherwise, baseline values were considered to be missing. Measurements from the Run-in visit were not used as a baseline value. If more than one measurement was planned for a scheduled time point (e.g., blood pressure, heart rate), the mean value of the last set of measurements per time point prior to randomization was used as the baseline value.

Schedule of Assessments

Subjects were to return for visits at every month for Months 1 to 4, and then every 4 months until end of study.

A physical examination was conducted at Run-in, Screening, and every 12 months until end of study. Vitals signs and weight were collected at every visit. A 12-lead ECG was conducted at Run-in, Screening, baseline, and every 12 months until end of study. ECGs were also obtained in situations when blood potassium was >6.5 mmol/L. Hematology, hemoglobin A1c, serum chemistry, and urinalysis parameters were assessed at Run-in, Screening, and every visit except Month 1 (see Table 161for details). A limited chemistry panel for safety was performed at Month 1 and the up-titration visits (see Table 161 for details). Concomitant medications were recorded in the eCRF at every visit.

Endpoint assessments were performed at every visit starting with Visit 2 (Month 1). Confirmation of categorical renal endpoints (i.e., ≥40% or ≥57% decrease in eGFR compared to baseline, eGFR <15 mL/min/1.73 m^2) were done at least 4 weeks after the initial measurement as an unscheduled assessment.

Table 161. Laboratory Parameters

Parameter	Component
Hematology	White blood cell count (WBC), red blood cell count (RBC), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), MCH concentration (MCHC), platelets
Glycated hemoglobin ($HbA1_c$)	$HbA1_c$ only
Clinical chemistry (full)	Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), cholesterol (high density lipoprotein [HDL], low density lipoprotein [LDL], total), triglycerides, creatinine, eGFR (CKD-EPI), blood urea nitrogen, uric acid, bilirubin, sodium, serum potassium, magnesium, total protein, albumin, high-sensitivity C-reactive protein (hs-CRP)
Clinical chemistry (limited)	Serum creatinine, eGFR (CKD-EPI), sodium, serum potassium
Urinalysis	Urine albumin-to-creatinine ratio (UACR) will be measured in the first morning void urine samples collected at the subject's home on 3 consecutive days

Source: Clinical Study Protocol Version 3.0

15.5. Study Procedures

Randomization

Eligible patients were randomized ≤2 weeks after the Screening visit. Randomization was managed centrally using an interactive voice and web response system. Randomization was stratified by region (i.e., North America, Europe, Asia, Latin America, and other), type of albuminuria at Screening (i.e., "high" or "very high")), and eGFR at Screening (i.e., 25 to <45, 45 to <60, and ≥60 mL/min/1.73 m^2). The number of patients with "high" albuminuria and presence of diabetic retinopathy were capped at approximately 10% of the total population at Screening.

Blinding

The study was double-blinded using matching tablets in size, shape, and color for finerenone and placebo. The packaging and labeling were "designed to maintain the blinding of the investigator's team and patients." The study data remained blinded until database lock and authorization of data release according to standard operating procedures. In order to maintain the integrity of the study, SUSARS were waived from unblinding and expedited safety reporting if it represented one of the pre-specified disease-related efficacy endpoints.

Dosing

The starting dose for finerenone depended on the eGFR value at the Screening visit. Patients with an eGFR ≥25 to <60 mL/min/1.73 m^2 were started on finerenone 10 mg daily or placebo in addition to SOC, while patients with eGFR ≥60 mL/min/1.73 m^2 were started on finerenone 20 mg daily or placebo in addition to standard of care.

Dose up-titration could occur at any time once the patient had been on a stable dose for 4 weeks (±7 days), either at a regular visit or an up-titration visit. Up-titration could be performed if the following two conditions were met: (1) the potassium concentration (local laboratory value) was ≤4.8 mmol/L and (2) the eGFR decrease (local laboratory value) was less than 30% below the value measured at the last regular visit. An up-titration visit was performed after 4 weeks (±7 days) of up-titration of study drug (or restart of study drug after interruption of more than 7 days (see below)).

Dose down-titration could occur at any time during the study, including between-scheduled visits if required for safety reasons (see Table 162 for guidance for investigators). The study drug could be up-titrated again based on the conditions above. If the patient was already at the lower dose, the study drug could be interrupted at the investigator's discretion. If the study drug was interrupted for more than 7 days, the study drug was restarted at the lower dose (10 mg daily).

Table 162. Guidance for Investigators for Dose Adjustment for Safety Based on Blood Potassium

Blood potassium (mmol/L)	Action
First sample:	
≤4.8	If on lower dose of study drug, up-titrate to higher dose. If on higher dose of study drug, continue on the same dose.
4.9 to 5.5	Continue on the same dose.
>5.5	Withhold study drug and re-check potassium within 72 hours.
Second and subsequent samples:	
≤5.0	Re-start study drug at lower dose.
>5.0	Continue to withhold study drug; continue to monitor potassium and restart study drug at the lower dose only if potassium is ≤5.0

NOTE: lower dose = 10 mg once daily; higher dose = 20 mg once daily.

Source: Clinical Study Protocol Version 3.0

Compliance

To monitor compliance, the investigator was required to complete a drug dispensing log for each patient. Study drug was dispensed to each patient at each scheduled visit. Patients were instructed to return all of the study drug packaging, including unused study drug and empty packaging at each visit. Any discrepancies between the actual and expected amount returned were to be discussed with the patient at the time of the visit, and any explanation was to be documented in the source records.

Concomitant Medications and Treatment of Concomitant Medical Conditions

For at least 4 weeks prior to the Run-in visit, all patients must have been treated with either an ACE inhibitor or ARB or both. Starting with the Run-in visit, patients should have been treated only with an ACE inhibitor or ARB, but not both. For at least 4 weeks prior to the Screening visit, patients were to be treated with the maximum tolerated labeled dose (but not below the minimum labeled dose) of only an ACE inhibitor or an ARB, preferably without any adjustments to dose or choice of agent.

For at least 4 weeks prior to the Screening visit, patients were not to have changes to other antihypertensive or antiglycemic treatments.

Per international guidelines, the recommended target blood pressure for patients was <130/80; however, the value could vary for individual patients depending on their concomitant diseases and well-being. If blood pressure was considered uncontrolled by the Investigator during the study period, non-potassium sparing diuretics could be added as the first-choice to the treatment regimen. Thereafter, the addition of antihypertensive medication could be performed according to local guideline recommendations. Investigators were to follow local guidelines for the management of cardiovascular disease and CKD, including the use of statins, anti-platelets, and beta-blockers. The dosage of SOC therapies were not to be reduced solely to facilitate maintenance of study drug. Potassium supplementation and potassium-lowering agents (e.g., sodium polystyrene sulfate, calcium polystyrene sulfonate) were allowed to be prescribed during the study.

The following concomitant therapies were not permitted during the study: eplerenone, spironolactone, any renin inhibitor, any potassium-sparing diuretic, and potent cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitors or inducers.

Measures to Prevent Missing Data

All efforts were made to collect complete data for all patients randomized in the study. Study drug discontinuation for any reason did not constitute withdrawal from the study. Therefore, patients who discontinued study drug were expected to attend all protocol specified study visits and were encouraged to perform all assessments as stipulated in the visit schedule.

If a patient who discontinued study drug was unable to attend study visits in person, site staff kept in touch with the patient by means of phone contact with the subjects themselves or their pre-designated contacts, in accordance with the patient's study visit schedule. Data were continued to be collected on the patient's health status, including information on development of renal or cardiovascular complications and vital status. This data could also be collected from a healthcare provider, public or medical records, or other sources as available according to local guidelines.

When an event date was not known, the site investigator was asked to provide a best-estimate as to when the event occurred, as this was thought to be closer to the true date than a date produced by a computer algorithm.

Data from patients who prematurely terminated the study was used to the maximum extent possible. All missing or partial data were presented in the patient data listing as recorded on the eCRF.

For patients who withdrew consent, sensitivity analyses were performed to assess the impact of potential informative censoring, including the use of different imputation rules for considering patients without an event of the primary composite endpoint as having an event or being censored.

Identification and Reporting of Potential Endpoints

Potential endpoint events were reported as "outcome events" in the eCRF by site investigators from randomization onwards until the last visit in the study for all study patients. Events that occurred between the end of study visit and the post-treatment visit in subjects who completed treatment at the end of study visit, were reported in the eCRF but were not subsequently

adjudicated by the CEC. Investigators were to refer to the "Endpoint Manual" for definitions of "outcome events" (see

below). If there was doubt as to whether an event was a potential "outcome event" or not, it was reported as a (S)AE. If an event was reported incorrectly (e.g., outcome event reported as an SAE), the sponsor's physicians were to identify the events and contact the site, if necessary.

Adjudication of Potential Endpoints Events

Table 163 lists all the endpoint events (i.e., "outcome events") that were reported to the CEC. All death and hospitalization cases were sent to the CEC for adjudication, regardless of whether the case was related to an "outcome event" or adverse event.

Table 163. Endpoint Events Reported to the Clinical Event Committee

- Kidney failure
- Decrease of eGFR of ≥40% from baseline, confirmed by at least one additional standardized measurement at least 4 weeks after the initial measurement
- Decrease of eGFR of ≥57% from baseline, confirmed by at least one additional standardized measurement at least 4 weeks after the initial measurement
- Decrease of eGFR to less than 15 mL/min/1.73m², confirmed by at least one additional standardized measurement at least 4 weeks after the initial measurement
- CV and renal death events
- Non-fatal myocardial infarction
- Non-fatal stroke
- Hospitalization for heart failure
- Other CV hospitalization
- New onset of atrial fibrillation or atrial flutter

Source: Clinical Study Protocol Version 3.0
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate

The definitions for cardiovascular events were based on the 2014 ACC/AHA Key Data Elements and Definitions for CV Endpoints in Clinical Trials, and where applicable, the definitions were modified for study specific purposes.

The criteria for events that the Applicant is seeking claims for are listed below:

Kidney failure

- ESKD referred to kidney transplantation and peritoneal or hemodialysis that was necessary for at least 30 days and not known to recover at 90 days. When RRT was indicated for uremia, but not available, refused, or considered futile, then ESKD was diagnosed even without initiation of RRT.
- The CEC adjudicated positively cases of an eGFR of less than 15 mL/min/1.73 m2 with no confirmatory assessment when the patient died after initial decrease or the patient went on RRT

- Sustained decrease of eGFR ≥40% from baseline and sustained decrease of eGFR ≥57% from baseline over at least 4 weeks were both defined by evidence of at least two or more consecutive laboratory assessments. The date of onset of the eGFR decrease was considered to the be the date of the initial sample exceeding the threshold.

Renal death was defined as above.

- The RRT that was not initiated must have been directly related to the kidney failure to be considered for the "renal death" definition. RRT that was not initiated that was related to another disease condition (e.g., volume overload unrelated to kidney failure) was not considered as "renal death."
- If a patient was already on dialysis and decided to withdraw form dialysis, then death was considered to be due to withdrawal of dialysis and was not considered as "renal death."

Cardiovascular death

- Death due to acute myocardial infarction referred to a death by any cardiovascular mechanism within 30 days after a myocardial infarction and related to the immediate consequences of the myocardial infarction (e.g., progressive heart failure or recalcitrant arrhythmia), as well as death resulting from a procedure to treat a myocardial infarction or a complication of a myocardial infarction.
- Sudden cardiac death referred to a death that occurred unexpectedly not following an acute myocardial infarction and included witnessed death, death after cardiac arrest, and unwitnessed death in a patient seen alive and clinically stable ≤24 hours prior to being found death without any evidence supporting a specific non-cardiovascular cause of death.
- An undetermined death referred to patients who were not observed alive within 24 hours of death and without any other likely cause of death. Considering the targeted patient population and the competing causes of death, undetermined cause of death was considered to be cardiovascular death by default.
- Death due to heart failure referred to death in association with clinically worsening symptoms and/or signs of heart failure without evidence of another cause and not following an acute myocardial infarction.
- Death due to stroke referred to death within 30 days after a stroke that was either a direct consequence of the stroke or a complication of the stroke.
- Death due to cardiovascular procedures referred to death within 30 days caused by the immediate complications of a cardiovascular procedure. Death resulting from an elective coronary procedure to treat myocardial ischemia or death as a direct consequence of a cardiovascular investigation or procedure was considered as death due to a cardiovascular procedure.
- Death due to other cardiovascular causes referred to a cardiovascular death not included in the above categories. Non-stroke intracranial hemorrhage, non-procedural, or non-traumatic vascular rupture or hemorrhage causing cardiac tamponade were considered as cardiovascular hemorrhages.

Non-fatal cardiovascular events

- Non-fatal myocardial infarction referred to evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia.
- Non-fatal stroke referred to an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction, with symptom duration of 24 hours or more. Episodes lasting less than 24 hours could be considered as a stroke if there was an

intervention to abort the stroke. Stroke events in which the patient did not die within 30 days following the stroke or died from a cause that was not directly related to the stroke event were considered as "non-fatal stroke" as well.

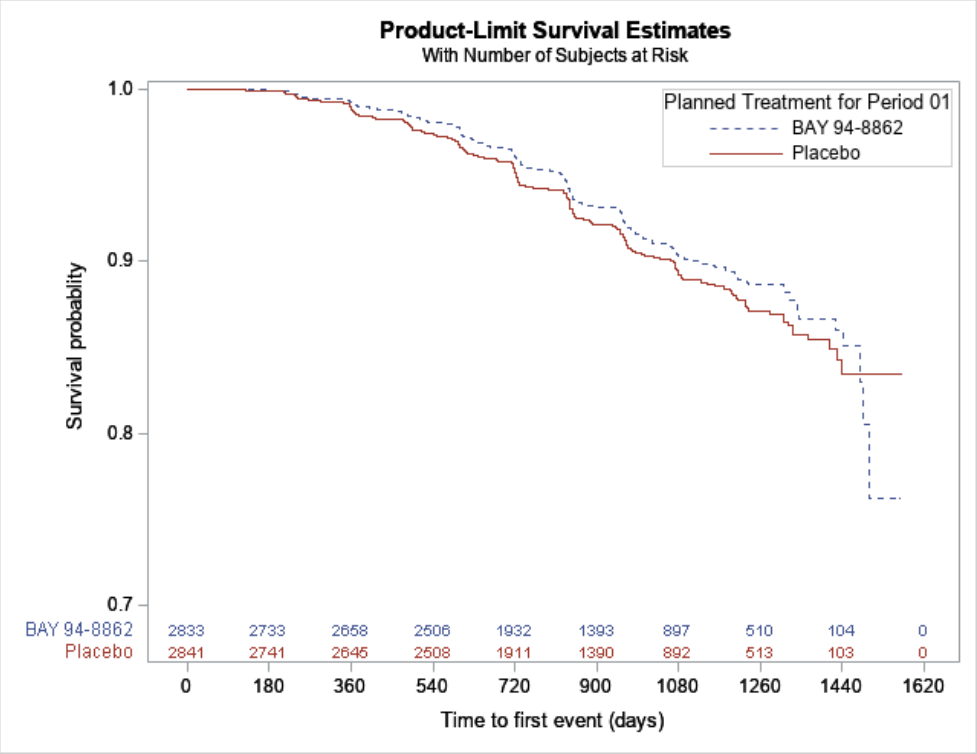
Hospitalization for heart failure referred to an event that met all of the following criteria:

- The patient was admitted to the hospital with a primary diagnosis of heart failure
- The patient's length of stay in the hospital extended for at least 24 hours
- The patient exhibited documented new symptoms or worsening symptoms due to heart failure on presentation, including at least one of the following: dyspnea, decreased exercise tolerance, fatigue, other symptoms of worsened end-organ perfusion or volume overload
- The patient has objective evidence of worsening heart failure consisting of at least two physical examination findings or one physical examination finding and at least one laboratory criterion
- The patient received initiation or intensification of treatment specifically for heart failure

16. Efficacy: Additional Information and Assessment

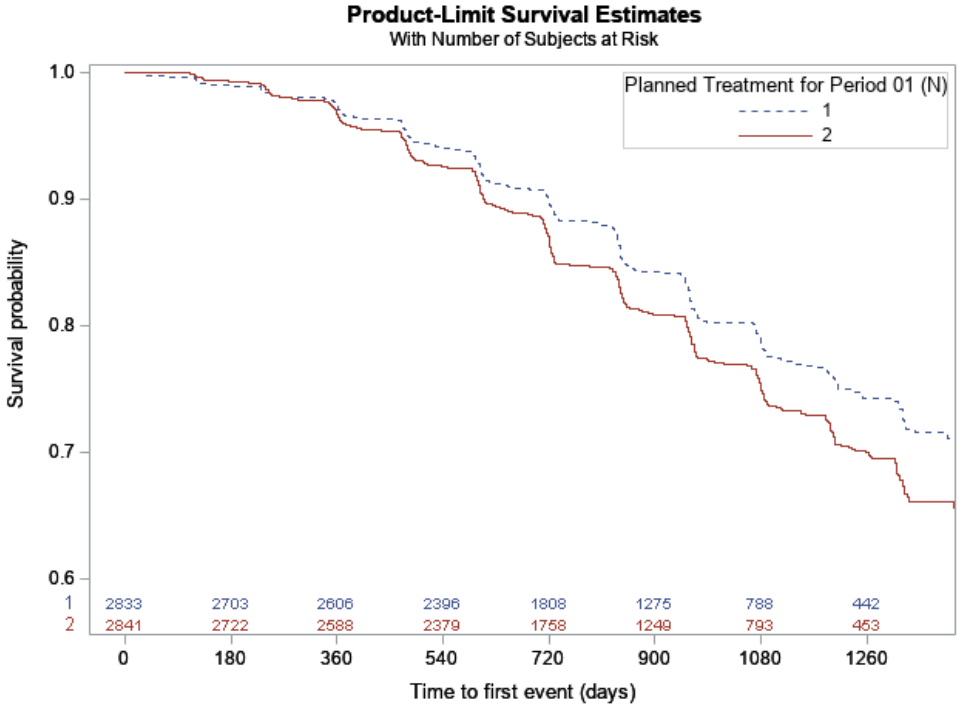
Kaplan Meier plots for the components of the primary and key secondary endpoint are shown below (Figure 50 to Figure 55).

Figure 50. Kaplan-Meier Plot for Kidney Failure (Full Analysis Set)



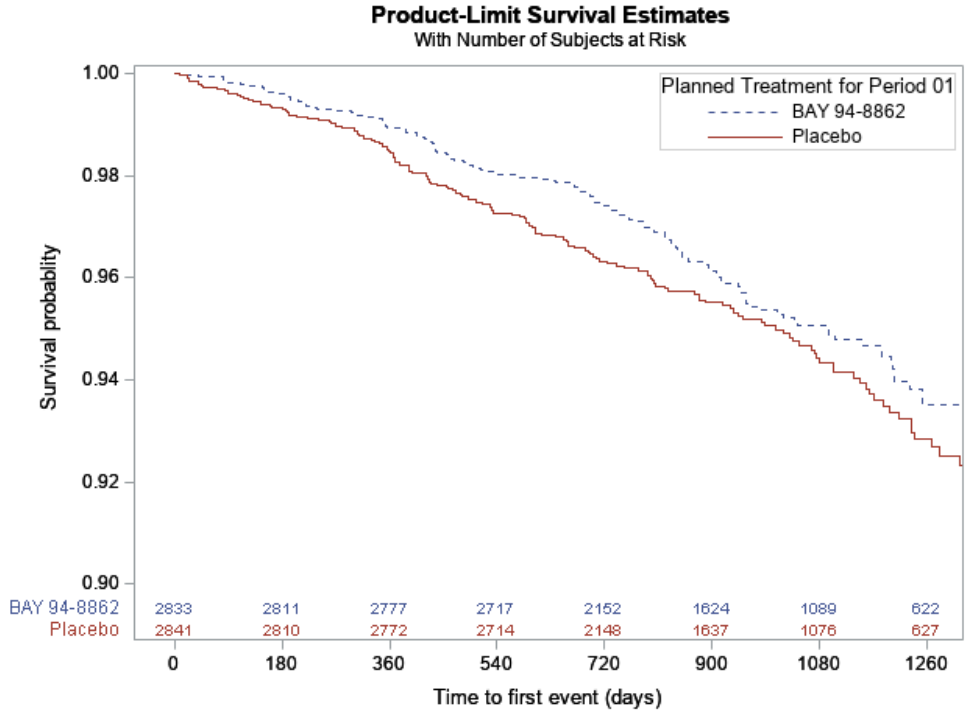
Source: Generated by statistical reviewer.

Figure 51. Kaplan-Meier Plot for Sustained Decrease of eGFR ≥40% From Baseline Over at Least 4 Weeks (Full Analysis Set)



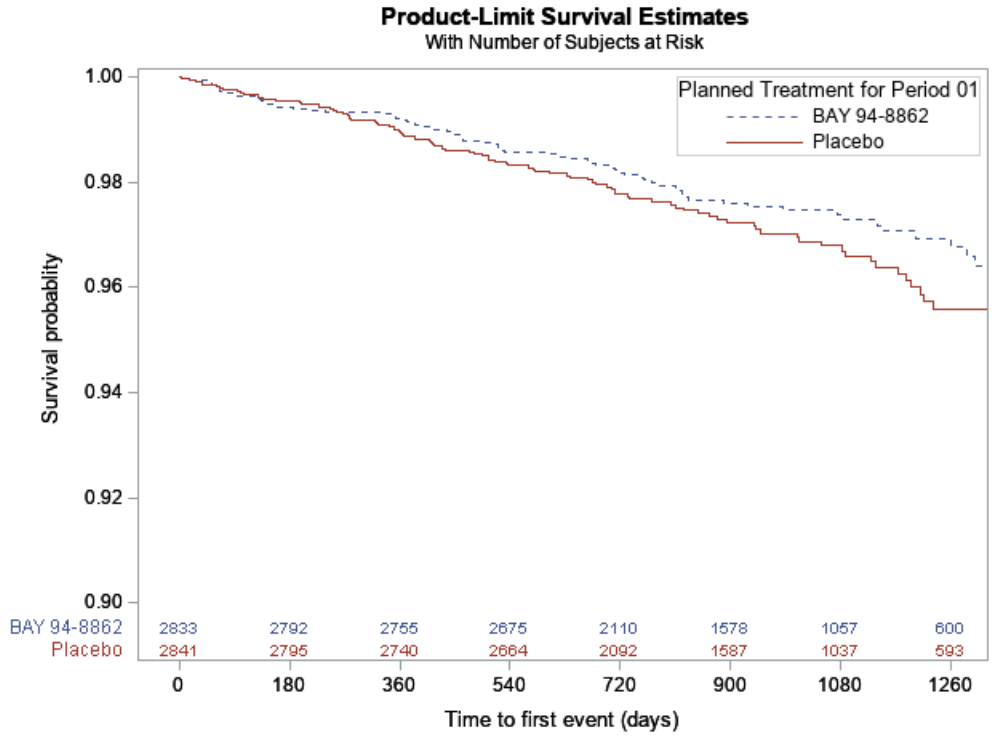
Source: Generated by statistical reviewer.
Abbreviations: eGFR, estimated glomerular filtration rate

Figure 52. Kaplan-Meier Plot for CV Death (Full Analysis Set)



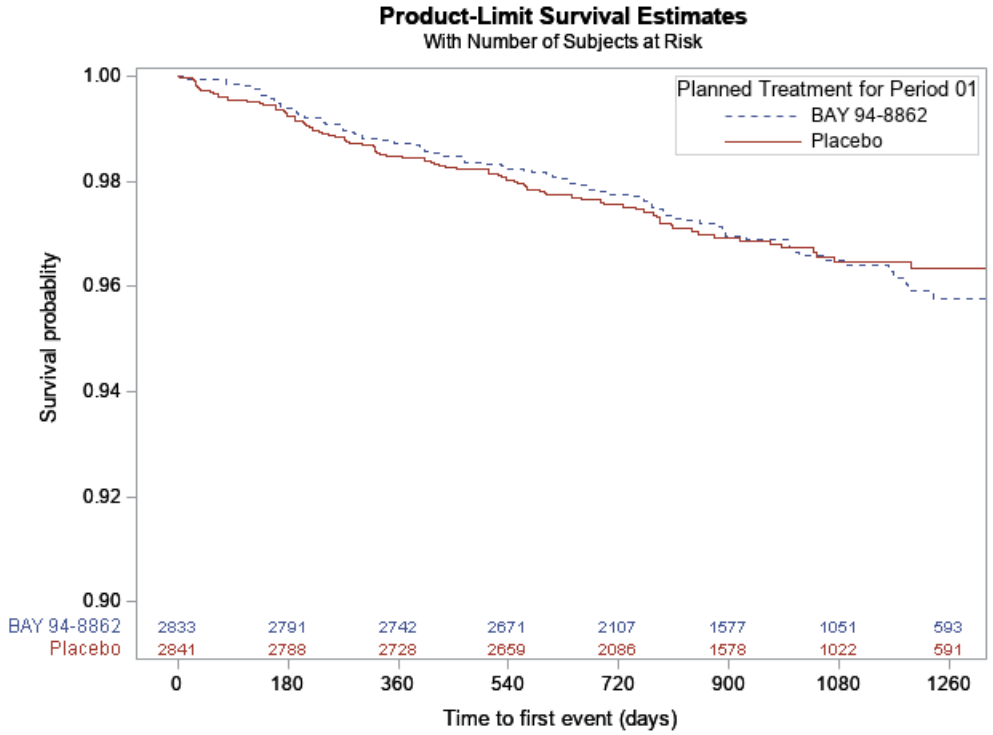
Source: Generated by statistical reviewer.
Abbreviations: CV, cardiovascular

Figure 53. Kaplan-Meier Plot for Non-Fatal MI (Full Analysis Set)



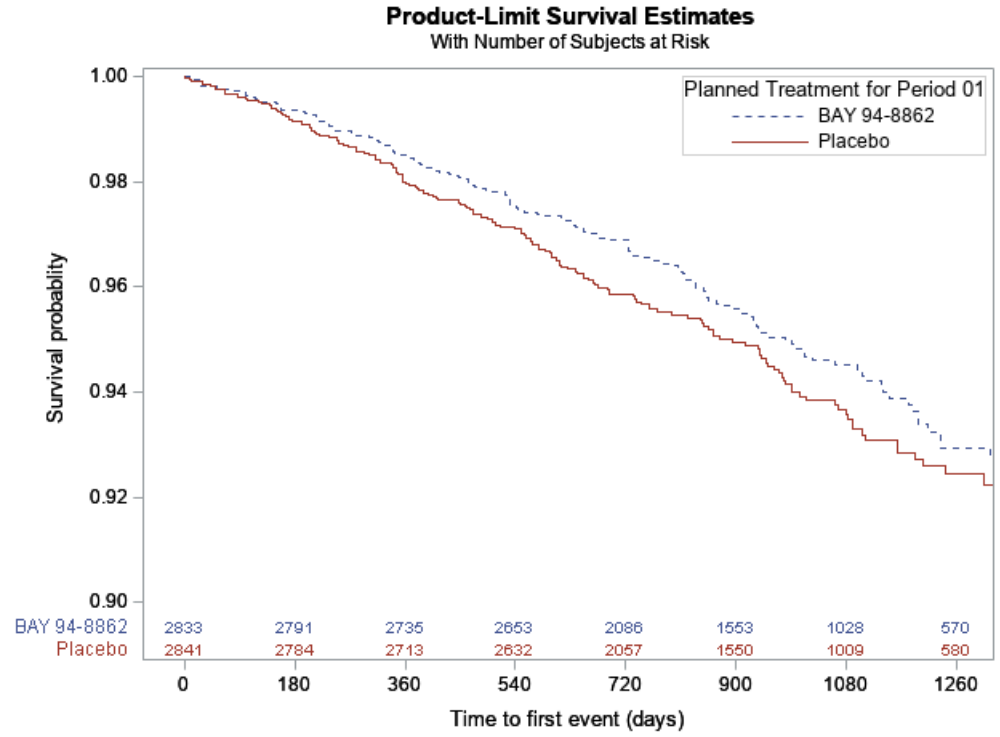
Source: Generated by statistical reviewer.
Abbreviations: MI, myocardial infarction

Figure 54. Kaplan-Meier Plot for Non-Fatal Stroke (Full Analysis Set)



Source: Generated by statistical reviewer.

Figure 55. Kaplan-Meier Plot for Hospitalization Due to Heart Failure (Full Analysis Set)



Source: Generated by statistical reviewer.

17. Clinical Safety: Additional Information and Assessment

Safety Data from Other Trials

Finerenone has been administered to over 1200 healthy volunteers and patients in twenty-seven phase 1 and five phase 2 studies at single doses ranging from ≤7.5 mg to 80 mg and multiple doses ranging from 10 mg daily to 40 mg daily. Review of safety data from these trials did not raise any new or additional safety concerns.

Subgroup Analyses of Key Adverse Events

Key Adverse Events Based on Baseline SGLT2 Inhibitor Use

Since the initiation of the finerenone development program, standard of care for the treatment of patients with type 2 diabetes and diabetic nephropathy has changed. In September 2019, canagliflozin, a SGLT-2 inhibitor, was approved to reduce the risk of end-stage kidney disease, doubling of serum creatinine, cardiovascular death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day. In April 2021, dapagliflozin, another member of the class, was approved to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression. As such, use of SGLT-2

inhibitors in patients with diabetic nephropathy is expected to increase over time. Further analyses were conducted to assess safety in patients receiving an SGLT2 inhibitor at baseline.

In the FIDELIO-DKD study, only 124 (4.4%) of patients randomized to finerenone and 135 (4.8%) of patients randomized to placebo were taking an SGLT2 inhibitor at baseline. Adverse events of interest, including hyperkalemia, hypotension and acute kidney, are shown by SGLT2 inhibitor use at baseline (yes or no) in the tables below. Although the amount of data on concomitant treatment with SGLT2 inhibitors and finerenone is limited, analyses of the available data do not raise concern from a safety perspective.

Table 164. Hyperkalemia Adverse Events Based on SGLT2 Inhibitor Use at Baseline, Safety Population, Trial 16244

Type of AE	n (%)	IR (per 100 pt-years)	n (%)	IR (per 100 pt-years)
SGLT-2 inhibitors use at baseline: YES	**Finerenone (N=124)**		**Placebo (N=135)**	
Any AE	10 (8.1%)	3.60	4 (3.0%)	1.28
Any study drug-related AE	5 (4.0%)	1.76	3 (2.2%)	0.96
Any AE leading to discontinuation of study drug	1 (0.8%)	0.35	1 (0.7%)	0.32
Any SAE	1 (0.8%)	0.35	0	0.00
Any study drug-related SAE	1 (0.8%)	0.35	0	0.00
Any SAE leading to discontinuation of study drug	1 (0.8%)	0.35	0	0.00
Any SAE leading to hospitalisation	1 (0.8%)	0.35	0	0.00
SGLT-2 inhibitors use at baseline: NO	**Finerenone (N=2703)**		**Placebo (N=2696)**	
Any AE	506 (18.7%)	9.45	251 (9.3%)	4.36
Any study drug-related AE	328 (12.1%)	5.92	132 (4.9%)	2.24
Any AE leading to discontinuation of study drug	63 (2.3%)	1.07	24 (0.9%)	0.40
Any SAE	43 (1.6%)	0.73	12 (0.4%)	0.20
Any study drug-related SAE	25 (0.9%)	0.43	5 (0.2%)	0.08
Any SAE leading to discontinuation of study drug	4 (0.1%)	0.07	1 (<0.1%)	0.02
Any SAE reported as life-threatening	3 (0.1%)	0.05	3 (0.1%)	0.05
Any SAE leading to hospitalisation	39 (1.4%)	0.67	8 (0.3%)	0.13

Source: Applicant response to FDA Request for Information, dated April 2, 2021
Abbreviations: AE, adverse event; IR, immediate release; SAE, serious adverse event; SGLT, sodium-glucose linked transporter

Table 165. Hypotension Adverse Events Based on SGLT2 Inhibitor Use at Baseline, Safety Population, Trial 16244

	n (%)	IR (per 100 pt-years)	n (%)	IR (per 100 pt-years)
SGLT-2 inhibitors use at baseline: YES	**Finerenone (N=124)**		**Placebo (N=135)**	
Any AE	6 (4.8%)	2.17	2 (1.5%)	0.64
Any study drug-related AE	2 (1.6%)	0.71	0	0.00
Any SAE	0	0.00	1 (0.7%)	0.32
Any SAE leading to hospitalisation	0	0.00	1 (0.7%)	0.32
SGLT-2 inhibitors use at baseline: NO	Finerenone (N=2703)		Placebo (N=2696)	
Any AE	129 (4.8%)	2.26	94 (3.5%)	1.60
Any study drug-related AE	42 (1.6%)	0.72	22 (0.8%)	0.37
Any AE leading to discontinuation of study drug	1 (<0.1%)	0.02	0	0.00
Any SAE	7 (0.3%)	0.12	4 (0.1%)	0.07
Any study drug-related SAE	3 (0.1%)	0.05	2 (<0.1%)	0.03
Any SAE reported as life-threatening	0	0.00	1 (<0.1%)	0.02
Any SAE leading to hospitalisation	6 (0.2%)	0.10	4 (0.1%)	0.07

Source: Applicant response to FDA Request for Information, dated April 2, 2021
Abbreviations: AE, adverse event; IR, immediate release; SAE, serious adverse event; SGLT, sodium-glucose linked transporter

Table 166. Acute Kidney Injury Adverse Events Based on SGLT2 Inhibitor Use at Baseline, Safety Population, Trial 16244

	n (%)	IR (per 100 pt-years)	n (%)	IR (per 100 pt-years)
SGLT-2 inhibitors use at baseline: YES	**Finerenone (N=124)**		**Placebo (N=135)**	
Any AE	1 (0.8%)	0.35	5 (3.7%)	1.62
Any SAE	0	0.00	2 (1.5%)	0.64
Any SAE leading to hospitalisation	0	0.00	2 (1.5%)	0.64
SGLT-2 inhibitors use at baseline: NO	**Finerenone (N=2703)**		**Placebo (N=2696)**	
Any AE	128 (4.7%)	2.21	131 (4.9%)	2.22
Any study drug-related AE	34 (1.3%)	0.58	18 (0.7%)	0.30
Any AE leading to discontinuation of study drug	5 (0.2%)	0.08	7 (0.3%)	0.12
Any SAE	56 (2.1%)	0.96	49 (1.8%)	0.82
Any study drug-related SAE	9 (0.3%)	0.15	6 (0.2%)	0.10
Any SAE leading to discontinuation of study drug	3 (0.1%)	0.05	5 (0.2%)	0.08
Any SAE with outcome death	0	0.00	1 (<0.1%)	0.02
Any SAE reported as life-threatening	0	0.00	1 (<0.1%)	0.02
Any SAE leading to hospitalisation	53 (2.0%)	0.90	45 (1.7%)	0.75

Source: Applicant response to FDA Request for Information, dated April 2, 2021
Abbreviations: AE, adverse event; IR, immediate release; SAE, serious adverse event; SGLT, sodium-glucose linked transporter

Key Adverse Events Based on Age, Sex, and Race

Subgroup analyses based on baseline age, sex, and race for the adverse events of hyperkalemia, hypotension, and acute kidney injury did not raise concern.

Additional Laboratory Analyses

Changes in eGFR, serum potassium, and serum sodium were analyzed after up-titration from 10 mg to 20 mg daily of finerenone in FIDELIO DKD. The values at the immediate visit after the dose up-titration (maximum 35 days) were compared to the values at the visit prior to the dose up-titration. As shown in Table 167, there was a small decrease in mean eGFR and small increase in mean serum potassium after dose up-titration of finerenone from 10 mg to 20 mg daily.

Table 167. Change in Laboratory Values After Dose Up-Titration, Trial 16244

Parameter Value Description	Finerenone N=1633 to 1655	Placebo N=1775 to 1801
Glomerular Filtration Rate, Estimated (mL/min/1.73m^2) in Blood - CKD EPI		
Mean (SD) value before dose change	41.5 (11.6)	42.8 (11.4)
Mean (SD) value after dose change	39.8 (11.7)	42.2 (11.9)
Mean (SD) difference between before and after	1.6 (6.6)	0.6 (6.9)
Median (min, max) difference between before and after	1.5 (-52.2, 36.4)	0.9 (-58.8, 60.3)
Subjects with pre- and post-titration data	1655	1801
Number of up-titration events with pre- and post-titration data	1865	1953

Parameter Value Description	Finerenone N=1633 to 1655	Placebo N=1775 to 1801
Potassium (mmol/L) in Serum		
Mean (SD) value before dose change	4.4 (0.4)	4.3 (0.4)
Mean (SD) value after dose change	4.6 (0.5)	4.3 (0.4)
Mean (SD) difference between before and after	-0.2 (0.5)	0 (0.4)
Median (min, max) difference between before and after	-0.2 (-2.1, 2.1)	0 (-2, 1.7)
Subjects with pre- and post-titration data	1645	1790
Number of up-titration events with pre- and post-titration data	1854	1940
Sodium (mmol/L) in Serum		
Mean (SD) value before dose change	139.1 (3.1)	139.4 (3.1)
Mean (SD) value after dose change	138.7 (3.3)	139.4 (2.9)
Mean (SD) difference between before and after	0.3 (2.9)	0 (2.6)
Median (min, max) difference between before and after	0 (-38, 14)	0 (-13, 12)
Subjects with pre- and post-titration data	1633	1775
Number of up-titration events with pre- and post-titration data	1836	1920

Source: adlb2.xpt from submission 0100 dated 2021/02/04; Software: R
The total number of safety population subjects in the finerenone and placebo arms was 2827 and 2831, respectively. The N in the table header row reflects those with data shown.
Up-titration events with a time interval between dose change and next measurement after dose change of 36 days or more were excluded from this analysis.
Abbreviations: min, minimum; max, maximum; SD, standard deviation

Additional Blood Pressure Analyses

Changes in systolic and diastolic blood pressure were analyzed after up-titration from 10 mg to 20 mg daily of finerenone in FIDELIO DKD. The values at the immediate visit after the dose up-titration (maximum 35 days) were compared to the values at the visit prior to the dose up-titration. On average, there was a small decrease in systolic and diastolic blood pressure after finerenone dose up-titration. See Table 168 for details.

Table 168. Change in Blood Pressure After Dose Up-Titration, Trial 16244

Parameter Value Description	Finerenone N=1625	Placebo N=1787
Systolic Blood Pressure		
Mean (SD) value before dose change	136.3 (15.6)	138.2 (15.1)
Mean (SD) value after dose change	134.1 (16)	138 (15.6)
Mean (SD) difference between before and after	2.2 (14.8)	0.1 (14.6)
Median (min, max) difference between before and after	1.7 (-56.7, 55.3)	0 (-54.7, 61.3)
Subjects with pre- and post-titration data	1625	1787
Number of up-titration events with pre- and post-titration data	1782	1887

Parameter Value Description	Finerenone N=1625	Placebo N=1787
Diastolic Blood Pressure		
Mean (SD) value before dose change	74.9 (10.1)	75.6 (9.9)
Mean (SD) value after dose change	73.8 (9.8)	75.2 (9.9)
Mean (SD) difference between before and after	1.1 (8.4)	0.4 (8.1)
Median (min, max) difference between before and after	1 (-36, 36.3)	0.3 (-36.7, 31)
Subjects with pre- and post-titration data	1625	1787
Number of up-titration events with pre- and post-titration data	1782	1887

Source: advs2.xpt from submission 0100 dated 2021/02/04; Software: R
The total number of safety population subjects in the finerenone and placebo arms was 2827 and 2831, respectively. The N in the table header row reflects those with data shown.
Up-titration events with a time interval between dose change and next measurement after dose change of 36 days or more were excluded from this analysis.
Abbreviations: min, minimum; max, maximum; SD, standard deviation

18. Mechanism of Action/Drug Resistance: Additional Information and Assessment

None.

19. Other Drug Development Considerations: Additional Information and Assessment

None.

20. Data Integrity-Related Consults (Office of Scientific Investigations, Other Inspections)

20.1. Independent Data Safety Monitoring Board Meeting Discussions

A summary of key DSMB meeting discussions is provided in Table 169.

Table 169. Key Data Safety Monitoring Board Meeting Discussions, Trial 16244

Date	Number of Patients Randomized	Issue/Discussion	
8/25/2015	0	DMC Kick-off Meeting	DMC Kick-off Meeting
3/21/2016	295	Per minutes, recruitment is ahead of schedule and the number of patients with treatment emergent AEs and with blood potassium >5.5 mmol/L and eGFR decrease of ≥30% from baseline is low.	Per minutes, recruitment is ahead of schedule and the number of patients with treatment emergent AEs and with blood potassium >5.5 mmol/L and eGFR decrease of ≥30% from baseline is low.
10/6/2016	1547	DMC charter updated to note that "DMC should not review efficacy data at the regular DMC meetings"	
3/16/2017	2367	Minutes note slower than expected recruitment, mainly due to "competing trials"	Minutes note slower than expected recruitment, mainly due to "competing trials"-
10/9/2017	3595	Minutes indicate a lower than expected annual event rate (primary and main secondary endpoint events). To minimize the risk of low annual rates of endpoint events, Bayer proposes to over-randomize the study and continue recruitment for 5 more months. The DMC has no objections.	Minutes indicate a lower than expected annual event rate (primary and main secondary endpoint events). To minimize the risk of low annual rates of endpoint events, Bayer proposes to over-randomize the study and continue recruitment for 5 more months. This was discussed by the DMC in the closed session (meeting minutes not available)

Date	Number of Patients Randomized	Issue/Discussion	
3/12/2018	4519	Per minutes, the "central lab (b) (4) (b) (4) changed the calibration method for the measurement of potassium values for all measurements taken on or after December 4, 2017. This change results in an average 0.2 mmol/L higher reported centrally [*sic*] potassium values compared to the 'old' values reported before…. As a consequence of this change in the calibration scheme…differences between potassium results of local and central lab measurements may increase." Post-Meeting, DMC members suggest that the Applicant "initiate a letter to the investigators to inform them about this change in the calibration scheme and its effects and to remind them about the guidance provided in the protocols already that local potassium values should be taken into account for dose adjustments." *Reviewer Note: The Applicant introduced an adjustment factor for potassium by "subtracting 0.2 mmol/L from the centrally measured potassium value under the new calibration scheme utilized from the December 4, 2018 onwards at (b) (4)." FDA agreed that a protocol amendment was not necessary to support the adjustment factor.*	Per minutes, the "central lab (b) (4) (b) (4) changed the calibration method for the measurement of potassium values for all measurements taken on or after December 4, 2017. This change results in an average 0.2 mmol/L higher reported centrally [*sic*] potassium values compared to the 'old' values reported before…. As a consequence of this change in the calibration scheme…differences between potassium results of local and central lab measurements may increase." Post-Meeting, DMC members suggest that the Applicant "initiate a letter to the investigators to inform them about this change in the calibration scheme and its effects and to remind them about the guidance provided in the protocols already that local potassium values should be taken into account for dose adjustments." *Reviewer Note: The Applicant introduced an adjustment factor for potassium by "subtracting 0.2 mmol/L from the centrally measured potassium value under the new calibration scheme utilized from the December 4, 2018 onwards at (b) (4)." FDA agreed that a protocol amendment was not necessary to support the adjustment factor.*
9/17/2018	5703	Applicant informs DMC that target randomization was revised from 4800 to 5800 given lower than expected event rate. Enrollment officially closed on June 8, 2018; trial on track to randomize 5800 patients. DMC notes that the study was "very well conducted."	Applicant informs DMC that target randomization was revised from 4800 to 5800 given lower than expected event rate. Enrollment officially closed on June 8, 2018; trial on track to randomize 5800 patients. DMC notes that the study was "very well conducted."
3/6/2019	5734	"There were no additional questions or comments from any of the DMC members"	

Date	Number of Patients Randomized	Issue/Discussion	
9/25/2019	5734	Applicant informs DMC that "…a small number of patients [60] had fraudulent activity/serious GCP deviations in the program. ExComm and FDA advice agreed with Bayer to remove these cases from all analyses….there was one site that was excluded in total, the other patients were single cases." Applicant also informs the DMC that the issue of the calibration method for potassium "is solved, all central lab potassium values that are present in the current database are correct and reliable." *Interim analysis (closed session):* "The DMC concluded that the renal events show a favorable trend for finerenone without statistical significance. According to the analysis conducted, the cardiovascular benefit is even higher than the renal benefit, but the associated p-values are clearly above 0.0027, the required level for the stopping rule for overwhelming efficacy….Therefore, the study should continue."	Applicant informs DMC that "…a small number of patients [60] had fraudulent activity/serious GCP deviations in the program. ExComm and FDA advice agreed with Bayer to remove these cases from all analyses….there was one site that was excluded in total, the other patients were single cases." Applicant also informs the DMC that the issue of the calibration method for potassium "is solved, all central lab potassium values that are present in the current database are correct and reliable." *Interim analysis (closed session):* "The DMC concluded that the renal events show a favorable trend for finerenone without statistical significance. According to the analysis conducted, the cardiovascular benefit is even higher than the renal benefit, but the associated p-values are clearly above 0.0027, the required level for the stopping rule for overwhelming efficacy….Therefore, the study should continue."
1/17/20	5734	Applicant informs the DMC that based on feedback from the FDA, they have decided to not include renal outcome events for statistical testing that occurred more than 150 days after the last eGFR measurement. "The reason for this censoring is the philosophy that outcome events (with all sub-components) should only be considered until the time where all required information is available." Seven of these renal outcome events were presented during the interim analysis of FIDELIO; the DMC "proposed having a calculation with and without these cases for DMC purposes."	Applicant informs the DMC that based on feedback from the FDA, they have decided to not include renal outcome events for statistical testing that occurred more than 150 days after the last eGFR measurement. "The reason for this censoring is the philosophy that outcome events (with all sub-components) should only be considered until the time where all required information is available." Seven of these renal outcome events were presented during the interim analysis of FIDELIO; the DMC "proposed having a calculation with and without these cases for DMC purposes."

Abbreviations: AE, adverse event; DMC, data monitoring committee; eGFR, estimated glomerular filtration rate; GCP, good clinical practice

21. Labeling Summary of Considerations and Key Additional Information

The following notable revisions to proposed labeling were discussed and agreed upon:

Indications and Usage

- The Applicant initially proposed an indication in "adult patients with chronic kidney disease and type 2 diabetes." The review team did not agree that the available data supported an indication for the proposed population since the trial entry criteria appeared to target patients with CKD thought to be caused by type 2 diabetes (as opposed to CKD of any etiology in patients with type 2 diabetes). After discussion with the Applicant, agreement was reached that the product would be indicated for use in "adult patients with chronic kidney disease associated with type 2 diabetes."

Warnings and Precautions

- The Applicant initially proposed Warnings and Precautions related to (b) (4) (b) (4) (b) (4). The review team thought that text in other places in the label adequately conveyed the critical information and did not believe the proposed Warnings and Precautions were warranted.
- The Applicant initially proposed a Warning and Precaution related to (b) (4) (b) (4). The review team did not believe that the proposed Warning and Precaution was supported by the available data; see discussion in Section 8.4 of this document.

Adverse Reactions

- The Applicant initially proposed to include (b) (4) (b) (4). The review team did not think that the proposed (b) (4) were needed since the risk of hyperkalemia was adequately addressed by other language in labeling. Some also voiced concern that the proposed (b) (4) could be falsely reassuring to prescribers.

Drug Interactions

- The Division proposed and the Applicant agreed to the addition of a subsection related to use with drugs that affect serum potassium.

Use in Specific Populations

- The Applicant proposed to include (b) (4) (b) (4). The review team considered the Applicant's proposal and the available data (see Section 8.4 of this document). Given the uncertainty about the applicability of the findings to humans, the review team concluded that labeling should inform prescribers about the findings (b) (4) (b) (4)
- The Applicant proposed a subsection (b) (4). The team concluded that the subsection was unnecessary (b) (4) (b) (4).

Clinical Studies

- The Applicant proposed to include (b) (4) (b) (4)

22. Postmarketing Requirements and Commitments

None.

23. Financial Disclosure

Table 170. Covered Clinical Studies: FIDELIO-CKD (16244)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1023 principal and sub-investigators		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The FIDELIO-DKD trial was a large, randomized, double-blind, placebo-controlled, multicenter trial with an objective primary endpoint. There were 3 investigators with disclosable financial interests/arrangements: (b) (6) (b) (6). Dr. (b) (6) was listed as a sponsor employee and was noted to have "contracts with Bayer less than USD 50K." A relatively small proportion of patients were consented by each of these investigators. As such, the risk to data integrity is thought to be low.

24. References

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Greaves, P, 2012, Male Genital Tract. In: Histopathology of preclinical toxicity studies: interpretation and relevance in drug safety evaluation, 4th edition, New York, New York: Academic Press.

Kolkhof, P, M Delbeck, A Kretschmer, W Steinke, E Hartmann, L Barfacker, F Eitner, B Albrecht-Kupper, and S Schafer, 2014, Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury, J Cardiovasc Pharmacol, 64(1):69-78.

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Naegele, M, AF Hernandez, and F Ruschitzka, 2016, Finerenone in heart failure: walking a fine line, Eur Heart J, 37(27):2115-2117.

Tang, DI and NL Geller, 1999, Closed testing procedures for group sequential clinical trials with multiple endpoints, Biometrics, 55(4):1188-1192.

25. Review Team

Table 171. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory Project Manager	Anna Park
Nonclinical Reviewer	Philip Gatti
Nonclinical Team Leader	Xuan Chi
Office of Clinical Pharmacology Reviewer(s)	Brianna Cote
Office of Clinical Pharmacology Team Leader(s)	Sudharshan Hariharan
Clinical Reviewer	Rekha Kambhampati
Statistical Reviewer	Dali Zhou
Statistical Team Leader	Jialu Zhang
Cross-Disciplinary Team Leader and Deputy Division Director (clinical)	Aliza Thompson
Division Director (pharm/tox)	Todd Bourcier
Division Director (OCP)	Shirley Seo
Division Director (OB)	Mark Rothman
Office Director (or designated signatory authority)	Ellis Unger

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 172. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Mohan Sapru
Microbiology	N/A
OPDP	Samantha Bryant
OSI	Suyoung (Tina) Chang
OSE/DEPI	Margie Goulding
OSE/DMEPA	Mariette Aidoo
OSE/DRISK	Brian Caruth
OSE/DPV	Courtney Suggs

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

Table 172 Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Norman Stockbridge, M.D., Ph.D.	OND/DCN	Enter sections. ☐ Authored ☒ Approved
Division Director	**Signature:** Norman L. Stockbridge -S Digitally signed by Norman L. Stockbridge -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300068764, cn=Norman L. Stockbridge -S Date: 2021.07.08 15:18:26 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Deputy Division Director/ Cross-Disciplinary Team Lead	Aliza Thompson, M.D., M.S.	OND/DCN	Enter sections. ☐ Authored Section 1 ☐ Approved Clinical Sections
	Signature: Aliza M. Thompson -S Digitally signed by Aliza M. Thompson -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300423038, cn=Aliza M. Thompson -S Date: 2021.07.09 07:06:39 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical	Rekha Kambhampati, M.D.	OND/DCN	2, 3, 4, 6.2.1.1, 6.2.1.2, 6.2.1.3, 6.2.1.4, 7.2, 7.3, 7.4, 7.5, 7.6, 12, 15, 17, 20.1 ☒ Authored ☐ Approved
Reviewer	**Signature:** Rekha Kambhampati -S Digitally signed by Rekha Kambhampati -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0011837744, cn=Rekha Kambhampati -S Date: 2021.07.07 10:23:13 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Mark Rothmann, Ph.D.	OTS/OB/DBII	Enter sections. ☐ Authored ☒ Approved
Division Director	**Signature:** Mark D. Rothmann -S Digitally signed by Mark D. Rothmann -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300144907, cn=Mark D. Rothmann -S Date: 2021.06.30 08:42:19 -04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Jialu Zhang, Ph.D.	OTS/OB/DBII	6.2.1.5, 6.2.1.6, 16 ☐ Authored ☒ Approved
Team Leader	**Signature:** Jialu Zhang -S Digitally signed by Jialu Zhang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jialu Zhang -S, 0.9.2342.19200300.100.1.1=1300369843 Date: 2021.06.29 15:25:03 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Statistical	Dali Zhou, Ph.D.	OTS/OB/DBII	6.2.1.5, 6.2.1.6, 16 ☒ Authored ☐ Approved
Reviewer	**Signature:** Dali Zhou -S Digitally signed by Dali Zhou -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Dali Zhou -S, 0.9.2342.19200300.100.1.1=2002462232 Date: 2021.06.29 15:12:09 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Todd Bourcier, Ph.D.	OND/OCHEN/DPT	5.1, 7.1, 8.3, 8.4, 13.1. 13.2. ☐ Authored ☒ Approved
Division Director	**Signature:** Todd M. Bourcier -S Digitally signed by Todd M. Bourcier -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300235462, cn=Todd M. Bourcier -S Date: 2021.07.02 10:15:59 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Xuan Chi, Ph.D.	OND/OCHEN/DPT	5.1, 7.1, 8.3, 8.4, 13.1. 13.2. ☐ Authored ☒ Approved
Team Leader	**Signature:** Xuan Chi -S Digitally signed by Xuan Chi -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Xuan Chi -S, 0.9.2342.19200300.100.1.1=0014066742 Date: 2021.06.30 09:49:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Pharmacology/Toxicology	Philip Gatti, Ph.D.	OND/OCHEN/DPT	5.1, 7.1, 8.3, 8.4, 13.1. 13.2. ☒ Authored ☐ Approved
Reviewer	**Signature:** Philip J. Gatti -S Digitally signed by Philip J. Gatti -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2000323344, cn=Philip J. Gatti -S Date: 2021.06.30 09:44:08 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Shirley Seo, PhD	OTS/OCP/DCEP	5, 6.1, 8.1, 8.2, 14.3, 14.4 ☐ Authored ☒ Approved
Division Director	**Signature:** Shirley K. Seo -S Digitally signed by Shirley K. Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shirley K. Seo -S, 0.9.2342.19200300.100.1.1=1300365375 Date: 2021.06.29 16:47:28 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Sudharshan Hariharan, PhD	OTS/OCP/DCEP	5, 6.1, 8.1, 8.2, 14 ☐ Authored ☒ Approved
Team Leader	**Signature:** Shirley K. Seo -S Digitally signed by Shirley K. Seo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shirley K. Seo -S, 0.9.2342.19200300.100.1.1=1300365375 Date: 2021.06.30 10:22:31 -04'00' Shirley Seo, on behalf of Sudharshan Hariharan		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Brianna Cote, PharmD, PhD	OTS/OCP/DCEP	5, 6.1, 8.1, 8.2, 14.1, 14.2, 14.5 ☒ Authored ☐ Approved
Reviewer	**Signature:** Brianna M. Cote -S Digitally signed by Brianna M. Cote -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2003141450, cn=Brianna M. Cote -S Date: 2021.06.29 15:54:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Eliford Kitabi, PhD	OTS/OCP/DPM	6.1, 8.2, 14.3 ☒ Authored ☐ Approved
Reviewer	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.07.08 09:04:27 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Justin Earp, PhD	OTS/OCP/DPM	6.1, 8.2, 14.3 ☐ Authored ☒ Approved
Team Leader	**Signature:** Justin C. Earp -S Digitally signed by Justin C. Earp -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Justin C. Earp -S, 0.9.2342.19200300.100.1.1=1300436664 Date: 2021.06.29 15:09:00 -04'00'		

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Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Jianghong Fan, PhD	OTS/OCP/DPM	14.4 ☒ Authored ☐ Approved
Reviewer	**Signature:** Jianghong Fan -S Digitally signed by Jianghong Fan -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Jianghong Fan -S, 0.9.2342.19200300.100.1.1=2001454698 Date: 2021.06.30 10:13:42 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved[1]
Clinical Pharmacology	Xinyuan Zhang, PhD	OTS/OCP/DPM	14.4 ☐ Authored ☒ Approved
Team Leader	**Signature:** Xinyuan Zhang -S Digitally signed by Xinyuan Zhang S DN: c US o U S Government ou HHS ou FDA ou People cn X nyuan Zhang S 0 9 2342 19200300 100 1 1 2000431943 Date: 2021 06 29 19:50:22 04'00'		

[1] Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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ANNA J PARK
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 215341
Drug Name:	Finerenone (BAY 94-8862)
Indication:	To [(b) (4)] reduce the risk of [(b) (4)] [(b) (4)] CV death, non-fatal MI, [(b) (4)] and hospitalization for heart failure in adult patients with CKD and T2D
Studies:	Carcinogenicity Studies in Rats and Mice for 104 weeks
Applicant:	Study Sponsor: Bayer AG Toxicology 13342 Berlin GERMANY Testing Facility: [(b) (4)]
Documents Reviewed:	Electronic submission: Submitted on November 10 2020 Electronic data: Submitted on November 10 2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics - VI
Statistical Reviewer:	Dr. Hepei Chen
Concurring Reviewer:	Dr. Karl Lin
Medical Division:	Division of Pharmacology Toxicology for Cardiology, Hematology, Endocrinology & Nephrology
Reviewing Pharmacologist:	Dr. Philip Gatti
Keywords:	Carcinogenicity, Dose response

Table of Contents

1. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to determine the effects of the test article, BAY 94-8862, on the incidence and morphology of tumors following daily oral (gavage) administration to the rat and mouse for 104 weeks.

In this review the phrase "dose response relationship" refers to the linear component (trend) of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases.

2. Rat Study

Two separate experiments, one in male rats and one in female rats were conducted. As indicated in Table 1, in each of these two experiments there were three treated groups, one saline control group, and one vehicle control group. Three hundred Crl:CD1(ICR) BR rats of each sex were assigned randomly in size of 60 rats per group. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for male rats, and 1, 3, and 10 mg/kg/day for female rats, respectively. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively. The rats in the saline control group and the vehicle control groups were administrated with sterile physiological saline (0.9% NaCl) and the vehicle [Ethanol/Kolliphore HS 15®/Purified Water (10/40/50 v/v/v)], respectively, and handled for the same duration and in the same manner as the treated groups.

Table 1: Experimental Design in Rat Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)			
	Male	Female		Male (Group #)		Female (Group #)	
1	60	60	Vehicle control	0	Group 0	0	Group 0
2	60	60	Saline control	0	Group 1	0	Group 1
3	60	60	BAY 94-8862 Low	2	Group 3	1	Group 2
4	60	60	BAY 94-8862 Mid	6	Group 5	3	Group 4
5	60	60	BAY 94-8862 High	20	Group 7	10	Group 6

All animals were observed at the beginning and the end of the working day for signs of ill health or overt toxicity. Each animal was given a detailed physical examination, including palpation for tissue masses, on Day 1 of the predose phase and at weekly intervals during the dosing phase. An individual record of the clinical condition of each animal was maintained. All carcinogenicity animals were subject to necropsy. All carcinogenicity animals that died or were sacrificed following the commencement of the scheduled necropsies were considered to have completed the study and were marked as terminal sacrifice. The scheduled necropsies were performed during Weeks 105 and 106 of the dosing phase after an overnight period without food and were carried out in replicate order (similar numbers of animals from each group sacrificed on each day). Each carcinogenicity animal was administered isoflurane anesthesia. All tissues specified in the tissue list in the protocol from each carcinogenicity animal, including carcinogenicity decedents, were examined microscopically by the Contributing Scientist for Anatomic Pathology. Following completion of the primary microscopic evaluation, an independent peer review evaluation was performed by the Sponsor.

2.1. Sponsor's analyses

2.1.1. Survival analysis

In the sponsor's report, tests to compare survival were performed with a two-sided risk for increasing and decreasing mortality with dose. Tests were performed for dose response (vehicle control and treated groups only) and for the saline control and each treated group against the vehicle control group using Kaplan-Meier product-limit estimates, along with log-rank and Wilcoxon tests. These were performed using the LIFETEST procedure in SAS. Dose group was included as the strata. Animals with a death or sacrifice status recorded as a planned sacrifice (interim or terminal) or an accidental death were censored in the analysis. The time to death or sacrifice (in weeks) was the dependent variable, and was calculated as below. time to death (weeks) = integer part of ([day of death - 1] / 7) + 1)

Sponsor's findings:

The sponsor's analysis showed that the numbers of rats surviving to their terminal necropsy were 39 (65%), 41 (68%), 43 (72%), 33 (55%), and 40 (67%) in the vehicle control, the saline control, the low, mid, and high dose groups for male rats, respectively, and 41 (68%), 43 (72%), 42 (70%), 44 (73%), and 43 (72%) for female rats respectively. In the sponsor's analysis, no statistically significant findings were noted for both male and female rats.

2.1.2. Tumor data analysis

In the sponsor's analysis, only tumors from tissues that were listed in the protocol to be examined for all animals were analyzed. Tests to compare tumor incidence were performed with a one-sided risk for increasing incidence with dose. The saline and vehicle control groups were compared using two-sided tests. Tests were performed for dose response (vehicle control and treated groups only) and for the saline control and each treated group against the vehicle control group.

For tumors occurring in animals dying spontaneously or sacrificed in extremis during the study, the pathologist classified the context of observation as one of the following:
(1) Fatal: the tumor was a factor in the demise of the animal.
(2) Non-fatal: the tumor was not a factor in the demise of the animal.
(3) Uncertain.

Tumors (palpable and non-palpable) were analyzed by the IARC asymptotic fixed interval based prevalence test (Peto et al., 1980). The cut off points for the interval. based test were Weeks 0-52, 53-78, 79-92, 93 to before terminal sacrifice, and terminal sacrifice. Fatal and non-fatal tumors were analyzed together, with separate stratum for each. There were no tumors of uncertain context. The test was implemented using PROC MULTTEST in the SAS system. In the case of sparse tables (<10 total in a strata), the exact form of the test was used for that strata. Otherwise, the asymptotic version of the test was used.

Animals were assigned to the terminal sacrifice strata based on the death or sacrifice status recorded in the data, and were not assigned based on their week of necropsy. For all analyses of tumors, unadjusted P-values were reported.

Site or tumor combinations were also statistically analyzed. The criteria for combination were based on the work of McConnell et al. (McConnell et al., 1986) and as indicated by the study pathologist. Incidences of multiple-organ and combined neoplastic findings, such as hemangioma, fibrosarcoma, and endometrial stromal polyp were counted by animal, not by tissue type.

Adjustment for multiple testing:

In the sponsor's report, indication of a possible treatment effect was assessed on the basis of rare or common tumor type, in line with the current FDA guidelines (FDA Draft Guidance for Industry, 2001).

Sponsor's findings:

In the sponsor's report, no statistically significant ($p<0.05$) dose response relationship and pairwise comparisons between the treated groups and the vehicle control groups were noted in the tumor data for both male and female rats. One statistically significant difference between the vehicle control and the saline control was noted for the benign fibroadenoma of mammary gland (p-value = 0.0227) in the female rats.

2.2. Reviewer's analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing toxicologist, this reviewer independently performed the survival and tumor data analyses using the data provided by the sponsor electronically.

2.2.1. Survival analysis

In the reviewer's analysis, the survival distributions of rats in all five groups (Groups 1, 2, 3, 4, and 5) were estimated using the Kaplan-Meier product limit method. The dose response relationship was tested across Groups 1, 3, 4, and 5 using the likelihood ratio test, and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for all five groups in male and female rats, respectively. The intercurrent mortality data of all five groups and the results of the tests for dose response relationship and homogeneity of survivals for Groups 1, 3, 4, and 5 are given in Tables 1A and 1B in the appendix for male and female rats, respectively.

Reviewer's findings:

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were 39 (65%), 41 (68%), 43 (72%), 33 (55%), and 40 (67%) in the vehicle control, the saline control, the low, mid, and high dose groups for male rats, respectively, and 41 (68%), 43 (72%), 42 (70%), 44 (73%), and 43 (72%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

2.2.2. Tumor data analysis

The tumor data were analyzed for dose response relationships across the vehicle control group, and low, mid, and high dose groups, and pairwise comparisons of each of the three treated groups and the saline control group against the vehicle control group, using the Poly-k method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993).

In the ploy-k method, the adjustment for differences in mortality among treatment groups is made by modifying the number of animals at risk in the denominators in the calculations of overall tumor rates in the Cochran-Armitage test to reflect less-than-whole-animal contributions for animals that die without tumor before the end of the study (Bailer and Portier 1988). The modification is made by defining a new number of animals at risk for each treatment group. The number of animals at risk for the *i*-th treatment group R^* i is defined as $R^* i = \sum W ij$ where w *ij* is the weight for the *j*-th animal in the *i*-th treatment group, and the sum is over all animals in the group.

Bailer and Portier (1988) proposed the weight w *ij* as follows:

w*ij* = 1 to animals dying with the tumor, and

w*ij* = (t*ij* / tsacr)^3 to animals dying without the tumor,

where t*ij* is the time of death of the *j*-th animal in the *i*-th treatment group, and tsacr is the planned (or intended) time of terminal sacrifice. The above formulas imply that animals living up to the end of the planned terminal sacrifice date without developing any tumor will also be assigned w*ij* =1 since t*ij* = tsacr. Also animals developed the tumor type being tested before the end of the study will be assigned as w*ij* = 1.

Certain treatment groups of a study or the entire study may be terminated earlier than the planned (or intended) time of terminal sacrifice due to excessive mortalities. However, based on the principle of the Intention-to-treat (ITT) analysis in randomized trials, the tsacr should not be affected by the unplanned early terminations. The tsacr should always be equal to the planned (or intended) time of terminal sacrifice. For those animals that were sacrificed later than tsacr, regardless their actual terminal sacrifice time, tsacr was used as their time of terminal sacrifice in the analysis.

One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data.

Multiple testing adjustment:

For the adjustment of multiple testing, this reviewer used the methodologies suggested in the FDA guidance for statistical design and analysis of carcinogenicity studies (2001). For dose response relationship tests, the guidance suggests the use of test levels of α=0.005 for common tumors and α=0.025 for rare tumors for a submission with two species where both are two-years studies, in order to keep the false-positive rate at the nominal level of approximately 10%. For multiple pairwise comparisons of treated group with control, the guidance suggests the use of test levels of α=0.01 for common tumors and α=0.05 for rare tumors, in order to keep the false-positive rate at the nominal level of approximately 10% for both submissions with two or one species.

A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%.

However, if the background information for the common or rare tumor is not available, the number of animals bearing tumors in the vehicle control group in the present study was used to determine the common or rare tumor status in the review report.

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 2A and 2B in the appendix for male and female rats, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 2.

Table 2: Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle control Group in Rats

		Vehicle (VC)	Low (L)	Mid (M)	High (H)	Saline (SC)
		0 mg	2 mg	6 mg	20 mg	0 mg
Organ name	Tumor name	P - Trend	P - VC vs. L	P - VC vs. M	P - VC vs. H	P - VC vs. SC
Male						
Thyroid	B-Follicular Cell Adenoma	2/60 (56)	3/60 (53)	0/60 (48)	6/60 (53)	1/60 (53)
		0.0343 @	0.4737	1.0000	0.1181	0.8680
	M-Follicular Cell Carcinoma	0/60 (56)	1/60 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.3067	0.4862	NC	0.4862	NC
	B-Follicular Cell Adenoma/ M-Follicular Cell Carcinoma	2/60 (56)	4/60 (53)	0/60 (48)	7/60 (53)	1/60 (53)
		0.0245 @	0.3134	1.0000	0.0684	0.8680
		0 mg	1 mg	3 mg	10 mg	0 mg
Female						
Mammary Gland	B-Fibroadenoma	4/58 (50) [&]	7/59 (51)	3/59 (53)	7/57 (51)	14/59 (54)
		0.2413	0.2740	0.8051	0.2740	0.0142 @
Pituitary	B-Adenoma, Pars Distalis	29/60 (55)	34/60 (53)	25/60 (56)	27/60 (56)	40/60 (57)
		0.8461	0.1566	0.8513	0.7470	0.0440 @
	B-Adenoma, Pars Intermedia	0/60 (52)	1/60 (50)	0/60 (52)	1/60 (52)	1/60 (54)
		0.3140	0.4902	NC	0.5000	0.5094
	B-Adenoma, Pars Distalis/ B-Adenoma, Pars Intermedia	29/60 (55)	35/60 (53)	25/60 (56)	28/60 (56)	41/60 (57)
		0.8125	0.1128	0.8513	0.6833	0.0282 @
Thyroid	B-C-Cell Adenoma	2/60 (52)	2/60 (50)	7/60 (52)	8/60 (52)	4/60 (54)
		0.0183 @	0.6763	0.0801	0.0462 @	0.3574
	M-C-Cell Carcinoma	0/60 (52)	0/60 (50)	1/60 (52)	0/60 (52)	0/60 (54)
		0.5049	NC	0.5000	NC	NC
	B-C-Cell Adenoma/ M-C-Cell Carcinoma	2/60 (52)	2/60 (50)	8/60 (52)	8/60 (52)	4/60 (54)
		0.0217 @	0.6763	0.0462 @	0.0462 @	0.3574

[&] X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.
@ = Not statistically significant in common tumor at 0.005 level for test of dose response relationship or at 0.01 level for test of pairwise comparisons;

Based on the criteria of adjustment for multiple testing discussed above, no statistically significant findings were noted in tumor data for both male and female rats.

3. Mouse Study

Two separate experiments, one in male mice and one in female mice were conducted. As indicated in Table 3, in the experiment of male mice there were four treated groups, one saline control group, and one vehicle control group, whereas in the experiment of female mice there were three treated groups, one saline control group, and one vehicle control group. Three hundred sixty and three hundred Crl:CD1(ICR) BR mice of male and female mice, respectively, were assigned randomly in size of 60 mice per group. The dose levels for the four treated groups of male mice were 1, 3, 10, and 30 mg/kg/day, and the dose levels for the three treated groups of female mice were 0.75, 2.5, and 7.5 mg/kg/day. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), mid-high (Group 5) and high (Group 6) dose groups for male mice, and low (Group 3), mid (Group 4), and high (Group 6) dose groups for female mice, respectively. The mice in the saline control group and the vehicle control groups were administrated with sterile physiological saline (0.9% NaCl) and the vehicle (aqueous 0.5% tylose), respectively, and handled for the same duration and in the same manner as the treated groups.

Table 3: Experimental Design in Mouse Study

Group No.	No. of Toxicity Animals		Test Material	Dosage Level (mg/kg/day)			
	Male	Female		Male (Group #)		Female (Group #)	
1	60	60	Vehicle control	0	Group 0	0	Group 0
2	60	60	Saline control	0	Group 1	0	Group 1
3	60	60	BAY 94-8862 Low	1	Group 3	0.75	Group 2
4	60	60	BAY 94-8862 Mid	3	Group 5	2.5	Group 4
5	60	60	BAY 94-8862 Mid-High	10	Group 7		
6	60	60	BAY 94-8862 High	30	Group 8	7.5	Group 6

The same clinical examinations, laboratory investigations and pathology procedures used in the rat study were also performed in the mouse study.

3.1. Sponsor's analyses

Because the mouse study was conducted by the same testing facility as the rat study, the sponsor used the same methodologies that were used for the analyses of the rat survival and tumor data.

3.1.1. Survival analysis

Sponsor's findings:

The sponsor's analysis showed that the numbers of mice surviving to their terminal necropsy were 38 (63%), 41 (68%), 42 (70%), 41 (68%), 39 (65%) and 40 (67%) in the vehicle control group, the saline control group, the low, mid, mid-high, and high dose groups for male mice, respectively, and 24 (40%), 29 (48%), 31 (52%), 26 (43%), and 26 (43%) for female mice respectively. There were no statistically significant findings in mortality was noted for both male or female mice.

3.1.2. Tumor data analysis

Multiple testing adjustment:

The same multiple testing adjustment used in the rat study was used in the mouse study.

Sponsor's findings:

In the sponsor's report, as indicated in Table 4, a statistically significant dose response relationship (p-value = 0.0002) was noted for benign Leydig cell adenoma in testis of male mice if this tumor is considered to be common. Statistically significant increases were noted for benign polyp glandular, and combined benign polyp glandular, benign polyp endometrial stromal and malignant sarcoma endometrial stromal in uterus of female mice (p-values = 0.0393 and 0.0073, respectively). No other statistically significant finding was noted for both male and female mice.

Table 4: Results of Statistical Analyses of Neoplastic Lesions in Mouse Study from Sponsor's Report

Tissue and Lesion	Rare or Common	Comparison	Incidence	P-value	FDA Interpretation
Testis B-Leydig cell adenoma	Common	Trend	2/60,1/60,3/60,0/60,9/60	0.0002	Significant (p<0.005)
		Group 1 v 9	2/60 v 9/60	0.0149	Not significant (p≥0.01)

Tissue and Lesion	Comparison	Incidence	P-value
Uterus B-Polyp, glandular	Group 1 v 2	0/60 v 4/60	0.0393
Uterus Combined B-Polyp, endometrial stromal/B-Polyp, glandular/M-Sarcoma, endometrial stromal	Group 1 v 2	3/60 v 14/60	0.0073

3.2. Reviewer's analyses

Similar to the rat study, this reviewer independently performed survival and tumor data analyses of mouse data to verify sponsor's analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

For the analysis of both the survival data and the tumor data in mice, this reviewer used similar methodologies that were used for the analyses of the rat survival and tumor data.

3.2.1. Survival analysis

Reviewer's findings:

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 38 (63%), 41 (68%), 42 (70%), 41 (68%), 39 (65%) and 40 (67%) in the vehicle control group, the saline control group, the low, mid, mid-high, and high dose groups for male mice, respectively, and 24 (40%), 29 (48%), 31 (52%), 26 (43%), and 26 (43%) for female mice respectively. There were no statistically significant findings in mortality was noted for both male or female mice.

3.2.2. Tumor data analysis

Reviewer's findings:

The tumor rates and the p-values of the tested tumor types are listed in Tables 4A and 4B in the appendix for male and female mice, respectively. The tumor types with p-values less than or equal to 0.05 for dose response relationship and/or pairwise comparisons of treated groups and vehicle control are reported in Table 5.

Based on the criteria of adjustment for multiple testing discussed above, a statistically significant dose response relationship (p-value = 0.0007) was noted for benign leydig cell adenoma in testis of male mice regardless this tumor's classification (rare or common). No other statistically significant finding was noted in the reviewer's analysis for both male and female mice.

Table 5. Summary Table of Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship and/or Pairwise Comparisons of Treated Groups and Vehicle control Group in Mice

		Vehicle (C)	Low (L)	Mid (M)	Mid-High (MH)	High (H)	Saline (S)
		0 mg	1 mg	3 mg	10 mg	30 mg	
Organ name	Tumor name	P-Trend	LP-LvsC	P-MvsC	P-MHvsC	P-HvsC	P-SvsC
Male							
Testis	B-Leydig Cell Adenoma	2/60 (50) [&]	1/60 (50)	3/60 (49)	0/60 (49)	9/60 (50)	1/60 (53)
		0.0007 $	0.8788	0.4903	1.0000	0.0256 x	0.8892

		Vehicle (VC)	Low (L)	Mid (M)	High (H)	Saline (SC)
		0 mg	0.75 mg	2.5 mg	7.5 mg	0 mg
Organ name	Tumor name	P - Trend	P - VC vs. L	P - VC vs. M	P - VC vs. H	P - VC vs. SC
Female						
Uterus	M-Sarcoma, Endometrial	3/60 (43)	12/60 (51)	3/60 (47)	4/60 (42)	10/60 (44)
	Stro*/B-Polyp, Endometrial	0.7851	0.0263 @	0.7033	0.4866	0.0376 @

[&] X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed
NC = Not calculable.
$ = Statistically significant in common tumor at 0.005 level for test of dose response relationship;
@ = Not statistically significant in common tumor at 0.01 level for test of pairwise comparisons;

4. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in rats and one in mice. These studies were to determine the effects of the test article, BAY 94-8862, on the incidence and morphology of tumors following daily oral (gavage) administration to the rat and mouse for 104 weeks.

Rat Study:

Two separate experiments, one in male rats and one in female rats were conducted. In each of these two experiments there were three treated groups, one saline control group, and one vehicle control group. Three hundred Crl:CD1(ICR) BR rats of each sex were assigned randomly in size of 60 rats per group. The dose levels for the three treated groups were 2, 6, and 20 mg/kg/day for male rats, and 1, 3, and 10 mg/kg/day for female rats, respectively. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), and high (Group 5) dose groups, respectively.

The reviewer's analysis showed that the numbers of rats surviving to their terminal necropsy were

39 (65%), 41 (68%), 43 (72%), 33 (55%), and 40 (67%) in the vehicle control, the saline control, the low, mid, and high dose groups for male rats, respectively, and 41 (68%), 43 (72%), 42 (70%), 44 (73%), and 43 (72%) for female rats respectively. No statistically significant dose response relationship and pairwise comparisons in mortality was noted for both male and female rats.

In the reviewer's analysis, no statistically significant findings were noted in tumor data for both male and female rats.

Mouse Study:

Two separate experiments, one in male mice and one in female mice were conducted. In the experiment of male mice there were four treated groups, one saline control group, and one vehicle control group, whereas in the experiment of female mice there were three treated groups, one saline control group, and one vehicle control group. Three hundred sixty and three hundred Crl:CD1(ICR) BR mice of male and female mice, respectively, were assigned randomly in size of 60 mice per group. The dose levels for the four treated groups of male mice were 1, 3, 10, and 30 mg/kg/day, and the dose levels for the three treated groups of female mice were 0.75, 2.5, and 7.5 mg/kg/day. In this review these dose groups were referred to as the low (Group 3), mid (Group 4), mid-high (Group 5) and high (Group 6) dose groups for male mice, and low (Group 3), mid (Group 4), and high (Group 6) dose groups for female mice, respectively.

The reviewer's analysis showed that the numbers of mice surviving to their terminal necropsy were 38 (63%), 41 (68%), 42 (70%), 41 (68%), 39 (65%) and 40 (67%) in the vehicle control group, the saline control group, the low, mid, mid-high, and high dose groups for male mice, respectively, and 24 (40%), 29 (48%), 31 (52%), 26 (43%), and 26 (43%) for female mice respectively. There were no statistically significant findings in mortality was noted for both male or female mice.

In the reviewer's analysis, a statistically significant dose response relationship (p-value = 0.0007) was noted for benign leydig cell adenoma in testis of male mice regardless this tumor's classification (rare or common). No other statistically significant finding was noted in the reviewer's analysis for both male and female mice

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5. Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle (VC)		Low (L)		Mid (M)		High (H)		Saline (SC)	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52			1	1.67	2	3.33	2	3.33	1	1.67
53 - 78			3	6.67	9	18.33	2	6.67	2	5.00
79 - 91	5	8.33	3	11.67	6	28.33	6	16.67	9	20.00
92 - 104	16	35.00	8	25.00	10	45.00	10	33.33	7	31.67
Accidental Death			2	3.33						
Terminal sacrifice	39	65.00	43	71.67	33	55.00	40	66.67	41	68.33
Total	60		60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle Control vs. Saline
Dose-Response (Likelihood Ratio)	0.8042	0.3623	0.1397	0.9888	0.8833
Homogeneity (Log-Rank)	0.1091	0.3592	0.1352	0.9887	0.8822

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle (VC)		Low (L)		Mid (M)		High (H)		Saline (SC)	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	3	5.00	1	1.67	1	1.67	1	1.67	1	1.67
53 - 78	3	10.00	2	5.00	2	5.00	5	10.00	1	3.33
79 - 91	6	20.00	5	13.33	4	11.67	4	16.67	5	11.67
92 - 104	7	31.67	6	23.33	7	23.33	6	26.67	9	26.67
Accidental Death			4	6.67	2	3.33	1	1.67	1	1.67
Terminal sacrifice	41	68.33	42	70.00	44	73.33	43	71.67	43	71.67
Total	60		60		60		60		60	

Test	All Dose Groups	Vehicle Control vs. Low	Vehicle Control vs. Mid	Vehicle Control vs. High	Vehicle Control vs. Saline
Dose-Response (Likelihood Ratio)	0.8343	0.4094	0.3543	0.5866	0.4903
Homogeneity (Log-Rank)	0.7831	0.4095	0.3537	0.5855	0.4881

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Adrenal	B-Benign Ganglioneuroma	0/60 (56)	1/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		0.7333	0.4862	NC	NC	NC
	B-Benign Phaeochromocytoma	2/60 (56)	1/60 (53)	3/60 (48)	3/60 (53)	3/60 (53)
		0.2272	0.8680	0.4267	0.4737	0.4737
	M-Malignant Phaeochromocyto*	0/60 (56)	1/60 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.6093	0.4862	0.4615	NC	NC
	B-Benign Phaeochromocytoma/ M-Malignant Phaeochromocyto*	2/60 (56)	2/60 (53)	4/60 (48)	3/60 (53)	3/60 (53)
		0.3248	0.6699	0.2688	0.4737	0.4737
	B-Cortical Adenoma	2/60 (56)	0/60 (53)	0/60 (48)	1/60 (53)	1/60 (53)
		0.5842	1.0000	1.0000	0.8680	0.8680
	M-Cortical Carcinoma	1/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000	1.0000
	B-Cortical Adenoma/ M-Cortical Carcinoma	3/60 (56)	0/60 (53)	0/60 (48)	1/60 (53)	1/60 (53)
		0.7047	1.0000	1.0000	0.9340	0.9340
Brain	B-Benign Tumor, Granular Ce*	1/60 (56)	2/60 (54)	2/60 (48)	1/60 (53)	2/60 (53)
		0.5843	0.4862	0.4419	0.7384	0.4792
	M-Malignant Granular Cell T*	0/60 (56)	0/60 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.4810	NC	0.4615	NC	NC
	B-Benign Tumor, Granular Ce*/ M-Malignant Granular	1/60 (56)	2/60 (54)	3/60 (48)	1/60 (53)	2/60 (53)
		0.6100	0.4862	0.2530	0.7384	0.4792
	M-Malignant Astrocytoma	1/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000	1.0000
	M-Malignant Glioma, Mixed	0/60 (56)	0/60 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.4810	NC	0.4615	NC	NC
	M-Malignant Meningioma	0/60 (56)	0/60 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.2524	NC	NC	0.4862	NC
Connective Tissue	B-Fibroma	0/60 (56)	1/60 (54)	0/60 (48)	0/60 (53)	0/60 (53)
		0.7346	0.4909	NC	NC	NC
	M-Malignant Schwannoma	0/60 (56)	0/60 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.4810	NC	0.4615	NC	NC
Ear	B-Haemangioma	0/60 (56)	0/60 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.2524	NC	NC	0.4862	NC
Ear, Inner	M-Squamous Cell Carcinoma	0/60 (56)	0/60 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.2524	NC	NC	0.4862	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Foot	B-Haemangioma	0/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	1/60 (53)
		NC	NC	NC	NC	0.4862
	B-Squamous Cell Papilloma	1/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000	1.0000
Haemolympho-Reticular System	M-Lymphocytic Leukaemia	0/60 (56)	0/60 (53)	1/60 (48)	1/60 (53)	0/60 (53)
		0.1787	NC	0.4615	0.4862	NC
	M-Malignant Lymphoma-Lympho*	2/60 (56)	1/60 (54)	1/60 (48)	0/60 (53)	0/60 (53)
		0.9154	0.8716	0.8478	1.0000	1.0000
	M-Malignant Lymphoma-Pleomo*	0/60 (56)	1/60 (54)	0/60 (48)	0/60 (53)	2/60 (53)
		0.7346	0.4909	NC	NC	0.2341
Jejunum	M-Adenocarcinoma	0/60 (56)	1/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		0.7333	0.4862	NC	NC	NC
Liver	B-Hepatocellular Adenoma	2/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	2/60 (53)
		1.0000	1.0000	1.0000	1.0000	0.6699
Lung	B-Bronchiolo-Alveolar Adeno*	0/60 (56)	1/60 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.6093	0.4862	0.4615	NC	NC
Lymph Node, Mesenteric	B-Haemangioma	1/60 (56)	1/60 (54)	1/60 (48)	0/60 (53)	0/59 (52)
		0.8123	0.7431	0.7125	1.0000	1.0000
Mammary Gland	B-Adenoma	1/25 (23)	0/28 (24)	0/31 (23)	0/28 (22)	0/25 (21)
		1.0000	1.0000	1.0000	1.0000	1.0000
Nasal Cavity	M-Carcinoma	1/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000	1.0000
Oral Cavity	B-Ameloblastoma	0/60 (56)	0/60 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.4810	NC	0.4615	NC	NC
Pancreas	B-Acinar Cell Adenoma	0/60 (56)	1/60 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		0.7333	0.4862	NC	NC	NC
	B-Islet Cell Adenoma	2/60 (56)	3/60 (53)	2/60 (48)	5/60 (53)	5/60 (53)
		0.1076	0.4737	0.6308	0.1966	0.1966
	B-Acinar Cell Adenoma/ B-Islet Cell Adenoma	2/60 (56)	4/60 (53)	2/60 (48)	5/60 (53)	5/60 (53)
		0.1508	0.3134	0.6308	0.1966	0.1966
Parathyroid	B-Adenoma	0/60 (56)	0/56 (50)	1/57 (45)	2/57 (50)	1/57 (50)
		0.0560	NC	0.4455	0.2201	0.4717

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Pituitary	B-Adenoma, Pars Distalis	25/60 (58)	18/60 (55)	27/60 (54)	18/59 (55)	27/60 (56)
		0.8138	0.9083	0.2941	0.9083	0.3596
	B-Adenoma, Pars Intermedia	2/60 (56)	1/60 (53)	0/60 (48)	0/59 (52)	2/60 (53)
		0.9815	0.8680	1.0000	1.0000	0.6699
	M-Carcinoma, Pars Distalis	0/60 (56)	0/60 (53)	0/60 (48)	0/59 (52)	2/60 (53)
		NC	NC	NC	NC	0.2341
	B-Adenoma, Pars Distalis/ B-Adenoma, Pars Intermedia/ M-Carcinoma, Pars Distalis	25/60 (58)	18/60 (55)	27/60 (54)	18/59 (55)	28/60 (56)
		0.8138	0.9083	0.2941	0.9083	0.2912
Preputial/ Clitoral Gland	B-Squamous Cell Papilloma	0/60 (56)	1/60 (53)	0/58 (46)	0/60 (53)	0/59 (52)
		0.7308	0.4862	NC	NC	NC
	M-Squamous Cell Carcinoma	1/60 (56)	1/60 (54)	0/58 (46)	2/60 (53)	4/59 (52)
		0.2393	0.7431	1.0000	0.4792	0.1593
	B-Squamous Cell Papilloma/ M-Squamous Cell Carcinoma	1/60 (56)	2/60 (54)	0/58 (46)	2/60 (53)	4/59 (52)
		0.3293	0.4862	1.0000	0.4792	0.1593
	M-Sarcoma - Nos	0/60 (56)	0/60 (53)	1/58 (46)	1/60 (53)	1/59 (52)
		0.1773	NC	0.4510	0.4862	0.4815

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Skin/Subcutis	B-Benign Basal Cell Tumour	0/60 (56)	0/59 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.2524	NC	NC	0.4862	NC
	B-Benign Hair Follicle Tumo*	2/60 (56)	4/59 (54)	1/60 (48)	0/60 (53)	2/60 (53)
		0.9684	0.3221	0.8478	1.0000	0.6699
	B-Fibroma	1/60 (56)	3/59 (54)	1/60 (48)	2/60 (53)	2/60 (53)
		0.4317	0.2954	0.7125	0.4792	0.4792
	M-Fibrosarcoma	0/60 (56)	1/59 (54)	1/60 (48)	0/60 (53)	2/60 (53)
		0.6081	0.4909	0.4615	NC	0.2341
	B-Fibroma/M-Fibrosarcoma	1/60 (56)	4/59 (55)	2/60 (48)	2/60 (53)	4/60 (53)
		0.5221	0.1762	0.4419	0.4792	0.1649
	B-Keratoacanthoma	6/60 (56)	2/59 (53)	1/60 (48)	1/60 (53)	3/60 (53)
		0.9603	0.9639	0.9891	0.9922	0.9056
	B-Lipoma	1/60 (56)	0/59 (53)	0/60 (48)	1/60 (53)	1/60 (53)
		0.4420	1.0000	1.0000	0.7384	0.7384
	M-Histiocytic Sarcoma	1/60 (56)	0/59 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000	1.0000
	M-Malignant Schwannoma	1/60 (56)	0/59 (53)	0/60 (48)	0/60 (53)	0/60 (53)
		1.0000	1.0000	1.0000	1.0000	1.0000
	M-Sarcoma Nos	0/60 (56)	0/59 (53)	0/60 (48)	0/60 (53)	1/60 (53)
		NC	NC	NC	NC	0.4862
	B-Squamous Cell Papilloma	1/60 (56)	1/59 (53)	1/60 (48)	0/60 (53)	0/60 (53)
		0.8134	0.7384	0.7125	1.0000	1.0000
	M-Squamous Cell Carcinoma	0/60 (56)	1/59 (54)	1/60 (48)	1/60 (53)	0/60 (53)
		0.2840	0.4909	0.4615	0.4862	NC
	M-Squamous Cell Carcinoma/ B-Squamous Cell Papilloma	7/60 (56)	4/59 (54)	3/60 (48)	2/60 (53)	3/60 (53)
		0.9384	0.8871	0.9233	0.9806	0.9438
Testis	B-Leydig Cell Adenoma	3/60 (56)	1/59 (53)	1/60 (48)	1/60 (53)	1/60 (53)
		0.7788	0.9340	0.9201	0.9340	0.9340

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 2 mg P - VC vs. L	Mid (M) 6 mg P - VC vs. M	High (H) 20 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Thymus	B-Benign Thymoma	2/59 (55)	0/58 (51)	1/60 (48)	2/59 (52)	2/58 (51)
		0.2948	1.0000	0.8517	0.6696	0.6620
	M-Malignant Thymoma	0/59 (55)	0/58 (51)	0/60 (48)	0/59 (52)	1/58 (51)
		NC	NC	NC	NC	0.4811
	B-Benign Thymoma/ M-Malignant Thymoma	2/59 (55)	0/58 (51)	1/60 (48)	2/59 (52)	3/58 (51)
		0.2948	1.0000	0.8517	0.6696	0.4640
	M-Carcinoma, Nos	0/59 (55)	1/58 (51)	0/60 (48)	0/59 (52)	0/58 (51)
		0.7330	0.4811	NC	NC	NC
	M-Fibrosarcoma, Pleomorphic	0/59 (55)	0/58 (51)	0/60 (48)	0/59 (52)	1/58 (52)
		NC	NC	NC	NC	0.4860
Thyroid	B-C-Cell Adenoma	8/60 (56)	7/60 (55)	6/60 (48)	12/60 (53)	6/60 (53)
		0.0714	0.6969	0.7082	0.1898	0.7722
	M-C-Cell Carcinoma	0/60 (56)	0/60 (53)	0/60 (48)	0/60 (53)	1/60 (53)
		NC	NC	NC	NC	0.4862
	B-C-Cell Adenoma/ M-C-Cell Carcinoma	8/60 (56)	7/60 (55)	6/60 (48)	12/60 (53)	7/60 (53)
		0.0714	0.6969	0.7082	0.1898	0.6694
	B-Follicular Cell Adenoma	2/60 (56)	3/60 (53)	0/60 (48)	6/60 (53)	1/60 (53)
		0.0343	0.4737	1.0000	0.1181	0.8680
	M-Follicular Cell Carcinoma	0/60 (56)	1/60 (53)	0/60 (48)	1/60 (53)	0/60 (53)
		0.3067	0.4862	NC	0.4862	NC
	B-Follicular Cell Adenoma/ M-Follicular Cell Carcin	2/60 (56)	4/60 (53)	0/60 (48)	7/60 (53)	1/60 (53)
		0.0245	0.3134	1.0000	0.0684	0.8680

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 1 mg P - VC vs. L	Mid (M) 3 mg P - VC vs. M	High (H) 10 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Adrenal	B-Benign Phaeochromocytoma	0/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/60 (55)
		NC	NC	NC	NC	0.5140
	B-Cortical Adenoma	2/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	0/60 (54)
		1.0000	1.0000	1.0000	1.0000	1.0000
	M-Cortical Carcinoma	1/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	0/60 (54)
		1.0000	1.0000	1.0000	1.0000	1.0000
	B-Cortical Adenoma/ M-Cortical Carcinoma	3/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	0/60 (54)
		1.0000	1.0000	1.0000	1.0000	1.0000
Brain	B-Benign Tumor, Granular Ce*	0/60 (52)	2/60 (50)	1/60 (53)	2/60 (52)	0/60 (54)
		0.2028	0.2378	0.5048	0.2476	NC
Duodenum	B-Adenoma	0/60 (52)	0/60 (50)	1/60 (52)	0/60 (52)	0/60 (54)
		0.5049	NC	0.5000	NC	NC
Haemolympho-Reticular System	M-Malignant Lymphoma-Lympho*	0/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/60 (55)
		NC	NC	NC	NC	0.5140
Harderian Gland	B-Adenoma	0/60 (52)	1/60 (50)	0/60 (52)	0/60 (52)	0/60 (54)
		0.7476	0.4902	NC	NC	NC
Kidney	M-Nephroblastoma	0/60 (52)	1/60 (50)	0/60 (52)	0/60 (52)	0/60 (54)
		0.7476	0.4902	NC	NC	NC
Liver	B-Hepatocellular Adenoma	1/60 (52)	1/59 (49)	0/60 (52)	0/60 (52)	0/60 (54)
		0.9366	0.7374	1.0000	1.0000	1.0000
Lymph Node, Mesenteric	B-Haemangioma	1/60 (52)	0/59 (50)	1/60 (53)	0/60 (52)	0/60 (54)
		0.7584	1.0000	0.7571	1.0000	1.0000
Mammary Gland	B-Adenoma	3/58 (50)	1/59 (51)	0/59 (52)	2/57 (52)	3/59 (54)
		0.5047	0.9436	1.0000	0.8308	0.6969
	M-Adenocarcinoma	1/58 (50)	1/59 (50)	2/59 (53)	1/57 (51)	0/59 (54)
		0.5086	NC	0.5221	0.7574	1.0000
	B-Adenoma/ M-Adenocarcinoma	4/58 (50)	2/59 (51)	2/59 (53)	3/57 (52)	3/59 (54)
		0.5329	0.9022	0.9104	0.7977	0.8122
	B-Fibroadenoma	4/58 (50)	7/59 (51)	3/59 (53)	7/57 (51)	14/59 (54)
		0.2413	0.2740	0.8051	0.2740	0.0142

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 1 mg P - VC vs. L	Mid (M) 3 mg P - VC vs. M	High (H) 10 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Ovary	B-Benign Granulosa Cell Tum*	0/60 (52)	0/60 (50)	2/60 (52)	1/60 (52)	1/60 (54)
		0.2056	NC	0.2476	0.5000	0.5094
	B-Benign Mixed Sex Cord Str*	2/60 (52)	0/60 (50)	3/60 (53)	1/60 (53)	1/60 (54)
		0.5704	1.0000	0.5091	0.8821	0.8854
	M-Malignant Mixed Sex Cord *	0/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/60 (54)
		NC	NC	NC	NC	0.5094
	B-Benign Mixed Sex Cord Str*/ M-Malignant Mixed Sex	2/60 (52)	0/60 (50)	3/60 (53)	1/60 (53)	2/60 (54)
		0.5704	1.0000	0.5091	0.8821	0.7053
	B-Benign Thecoma	1/60 (52)	0/60 (50)	1/60 (52)	0/60 (52)	0/60 (54)
		0.7561	1.0000	NC	1.0000	1.0000
	B-Tubulostromal Adenoma	0/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/60 (54)
		NC	NC	NC	NC	0.5094
	M-Haemangiosarcoma	0/60 (52)	0/60 (50)	0/60 (52)	1/60 (52)	0/60 (54)
		0.2524	NC	NC	0.5000	NC
Pancreas	B-Islet Cell Adenoma	2/60 (52)	0/60 (50)	1/60 (53)	1/59 (52)	1/60 (55)
		0.5823	1.0000	0.8821	0.8786	0.8887
	M-Islet Cell Carcinoma	2/60 (52)	0/60 (50)	0/60 (52)	0/59 (52)	0/60 (54)
		1.0000	1.0000	1.0000	1.0000	1.0000
	B-Islet Cell Adenoma/ M-Islet Cell Carcinoma	4/60 (52)	0/60 (50)	1/60 (53)	1/59 (52)	1/60 (55)
		0.8201	1.0000	0.9731	0.9717	0.9756
Pituitary	B-Adenoma, Pars Distalis	29/60 (55)	34/60 (53)	25/60 (56)	27/60 (56)	40/60 (57)
		0.8461	0.1566	0.8513	0.7470	0.0440
	B-Adenoma, Pars Intermedia	0/60 (52)	1/60 (50)	0/60 (52)	1/60 (52)	1/60 (54)
		0.3140	0.4902	NC	0.5000	0.5094
	B-Adenoma, Pars Distalis/ B-Adenoma, Pars Intermedia	29/60 (55)	35/60 (53)	25/60 (56)	28/60 (56)	41/60 (57)
		0.8125	0.1128	0.8513	0.6833	0.0282
	M-Carcinoma, Pars Distalis	3/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/60 (54)
		1.0000	1.0000	1.0000	1.0000	0.9455
	M-Carcinoma, Pars Intermedia	1/60 (52)	0/60 (50)	0/60 (52)	1/60 (52)	0/60 (54)
		0.4421	1.0000	1.0000	NC	1.0000
	M-Carcinoma, Pars Distalis/ M-Carcinoma, Pars Intermedia	4/60 (52)	0/60 (50)	0/60 (52)	1/60 (52)	1/60 (54)
		0.8093	1.0000	1.0000	0.9717	0.9744
	B-Adenoma, Pars Distalis/ B-Adenoma, Pars Intermedia/ M-Carcinoma, Pars Distalis/ M-Carcinoma, Pars Intermedia	33/60 (55)	35/60 (53)	25/60 (56)	29/60 (56)	42/60 (57)
		0.8764	0.3265	0.9651	0.8560	0.0903

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 1 mg P - VC vs. L	Mid (M) 3 mg P - VC vs. M	High (H) 10 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Preputial/ Clitoral Gland	B-Benign Tumour, Granular C*	0/60 (52) 0.7451	1/58 (48) 0.4800	0/60 (52) NC	0/60 (52) NC	0/60 (54) NC
	M-Squamous Cell Carcinoma	1/60 (52) 1.0000	0/58 (48) 1.0000	0/60 (52) 1.0000	0/60 (52) 1.0000	0/60 (54) 1.0000
Skin/Subcutis	B-Benign Basal Cell Tumour	0/60 (52) 0.0628	0/60 (50) NC	0/60 (52) NC	2/60 (52) 0.2476	0/60 (54) NC
	B-Fibroma	0/60 (52) 0.2524	0/60 (50) NC	0/60 (52) NC	1/60 (52) 0.5000	0/60 (54) NC
	B-Keratoacanthoma	0/60 (52) 0.2524	0/60 (50) NC	0/60 (52) NC	1/60 (52) 0.5000	0/60 (54) NC
	M-Squamous Cell Carcinoma	0/60 (52) NC	0/60 (50) NC	0/60 (52) NC	0/60 (52) NC	1/60 (55) 0.5140
	B-Keratoacanthoma/ M-Squamous Cell Carcinoma	0/60 (52) 0.2524	0/60 (50) NC	0/60 (52) NC	1/60 (52) 0.5000	1/60 (55) 0.5140
	M-Liposarcoma	0/60 (52) 0.2560	0/60 (50) NC	0/60 (52) NC	1/60 (53) 0.5048	0/60 (54) NC
Thymus	B-Benign Thymoma	4/59 (51) 0.8340	4/60 (50) 0.6312	1/60 (53) 0.9745	2/59 (52) 0.9020	2/58 (52) 0.9020
	M-Malignant Thymoma	0/59 (51) 0.6328	1/60 (50) 0.4950	1/60 (53) 0.5096	0/59 (52) NC	0/58 (52) NC
	B-Benign Thymoma/ M-Malignant Thymoma	4/59 (51) 0.8726	5/60 (50) 0.4873	2/60 (53) 0.9061	2/59 (52) 0.9020	2/58 (52) 0.9020
Thyroid	B-C-Cell Adenoma	2/60 (52) 0.0183	2/60 (50) 0.6763	7/60 (52) 0.0801	8/60 (52) 0.0462	4/60 (54) 0.3574
	M-C-Cell Carcinoma	0/60 (52) 0.5049	0/60 (50) NC	1/60 (52) 0.5000	0/60 (52) NC	0/60 (54) NC
	B-C-Cell Adenoma/ M-C-Cell Carcinoma	2/60 (52) 0.0217	2/60 (50) 0.6763	8/60 (52) 0.0462	8/60 (52) 0.0462	4/60 (54) 0.3574
	B-Follicular Cell Adenoma	8/60 (52) 0.9972	6/60 (50) 0.7829	2/60 (52) 0.9921	1/60 (52) 0.9987	2/60 (54) 0.9933
	M-Follicular Cell Carcinoma	0/60 (52) 0.6280	1/60 (50) 0.4902	1/60 (52) 0.5000	0/60 (52) NC	0/60 (54) NC
	B-Follicular Cell Adenoma/ M-Follicular Cell Carcin	8/60 (52) 0.9976	7/60 (50) 0.6823	3/60 (52) 0.9742	1/60 (52) 0.9987	2/60 (54) 0.9933

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 2B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Rats (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 1 mg P - VC vs. L	Mid (M) 3 mg P - VC vs. M	High (H) 10 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Uterus	B-Polyp, Endometrial Stromal	5/60 (52)	7/60 (50)	8/60 (54)	5/60 (52)	5/60 (54)
		0.6496	0.3523	0.3028	NC	0.6532
	B-Polyp, Glandular	0/60 (52)	0/60 (50)	0/60 (52)	1/60 (52)	0/60 (54)
		0.2524	NC	NC	0.5000	NC
	M-Adenocarcinoma	2/60 (52)	2/60 (50)	3/60 (53)	0/60 (52)	0/60 (54)
		0.9194	0.6763	0.5091	1.0000	1.0000
	M-Malignant Schwannoma	0/60 (52)	3/60 (52)	0/60 (52)	2/60 (53)	0/60 (54)
		0.3052	0.1214	NC	0.2524	NC
	M-Stromal Sarcoma	0/60 (52)	1/60 (51)	0/60 (52)	0/60 (52)	0/60 (54)
		0.7488	0.4951	NC	NC	NC
	M-Tumor, Mixed Mullerian, M*	0/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/60 (54)
		NC	NC	NC	NC	0.5094
Vagina	M-Squamous Cell Carcinoma	0/60 (52)	0/60 (50)	0/60 (52)	0/60 (52)	1/59 (54)
		NC	NC	NC	NC	0.5094

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 3A: Intercurrent Mortality Rate in Male Mice

	Vehicle Control		1 mg/kg/day Low		3 mg/kg/day Mid		10 mg/kg/day Mid-High		30 mg/kg/day High		Saline Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	2	3.33	4	6.67	3	5.00	2	5.00	2	6.67
53 - 78	2	6.67	7	15.00	4	13.33	8	18.33	5	13.33	1	8.33
79 - 91	10	23.33	6	25.00	6	23.33	4	25.00	5	21.67	8	21.67
92 - 104	6	33.33	3	30.00	4	30.00	6	35.00	6	31.67	6	31.67
>105	.	.	.	.	.	.	.	.	1	1.67	2	3.33
Accidental Death	2	3.33	.	.	1	1.67	.	.	1	1.67	.	.
Terminal sacrifice	38	63.33	42	70.00	41	68.33	39	65.00	40	66.67	41	68.33
Total	60	.	60	.	60	.	60	.	60	.	60	.

Test	All Dose Groups	Vehicle vs. Low	Vehicle vs. Mid	Vehicle vs. Mid-high	Vehicle vs. High	Vehicle vs. Saline
Dose-Response (Likelihood Ratio)	0.9737	0.7664	0.7648	0.8095	0.8259	0.6994
Homogeneity (Log-Rank)	0.9798	0.7654	0.7634	0.8083	0.8252	0.6973

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 3B: Intercurrent Mortality Rate in Female Mice

	Vehicle Control		0.75 mg/kg/day Low		2.5 mg/kg/day Mid		7.5 mg/kg/day High		Saline Control	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	6	10.00	2	3.33	1	1.67	4	6.67	4	6.67
53 - 78	6	20.00	4	10.00	5	10.00	13	28.33	10	23.33
79 - 91	12	40.00	9	25.00	11	28.33	10	45.00	7	35.00
92 - 104	12	60.00	13	46.67	17	56.67	7	56.67	9	50.00
Accidental Death			1	1.67					1	1.67
Terminal sacrifice	24	40.00	31	51.67	26	43.33	26	43.33	29	48.33
Total	60		60		60		60		60	

Test	All Dose Groups	Vehicle vs. Low	Vehicle vs. Mid	Vehicle vs. High	Vehicle vs. Saline
Dose-Response (Likelihood Ratio)	0.4977	0.0932	0.4625	0.9073	0.4107
Homogeneity (Log-Rank)	0.3227	0.0899	0.4577	0.9066	0.4080

#All Cum. % Cumulative Percentage except for Terminal sacrifice;

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice

Organ name	Tumor name	Vehicle (C) 0 mg P-Trend	Low (L) 1 mg LP-LvsC	Mid (M) 3 mg P-MvsC	Mid-High (MH) 10 mg P-MHvsC	High (H) 30 mg P-HvsC	Saline (S) P-SvsC
Adrenal	B-Cortical Adenoma	3/59 (49) 0.9986	1/60 (50) 0.9437	0/59 (48) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	1/58 (51) 0.9460
	B-Subcapsular Cell Adenoma (113)	2/59 (49) 0.8477	4/60 (50) 0.3485	2/59 (48) 0.6836	2/60 (49) NC	1/60 (50) 0.8825	6/58 (52) 0.1546
	B-Subcapsular Cell Adenoma (733)	0/59 (49) NC	0/60 (50) NC	0/59 (48) NC	0/60 (49) NC	0/60 (50) NC	1/58 (51) 0.5100
	B-Subcapsular Cell Adenoma (734)	2/59 (49) 0.4761	1/60 (50) 0.8825	3/59 (49) 0.5000	1/60 (49) 0.8789	2/60 (50) 0.6990	2/58 (51) 0.7063
	B-Subcapsular Cell Adenoma	4/59 (49) 0.7752	5/60 (50) 0.5130	5/59 (49) 0.5000	3/60 (49) 0.7822	3/60 (50) 0.7904	9/58 (52) 0.1413
Bone, Other	M-Osteosarcoma	0/60 (50) NC	0/60 (50) NC	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	1/60 (53) 0.5146
Brain	M-Malignant Meningioma	0/60 (50) 0.7992	1/60 (51) 0.5050	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	1/60 (53) 0.5146
Connective Tissue	M-Haemangiosarcoma	0/60 (50) 0.7984	1/60 (50) 0.5000	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
	M-Sarcoma Nos	0/60 (50) 0.5984	0/60 (50) NC	1/60 (50) 0.5000	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
Duodenum	B-Leiomyoma	0/59 (49) 0.2033	0/59 (49) NC	0/59 (49) NC	0/60 (49) NC	1/59 (50) 0.5051	0/59 (52) NC
Ear	B-Fibroma	0/54 (44) 0.6076	0/58 (49) NC	1/60 (50) 0.5319	0/60 (49) NC	0/55 (45) NC	0/59 (52) NC
	M-Sarcoma, Histiocytic	1/54 (44) 1.0000	0/58 (49) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/55 (45) 1.0000	0/59 (52) 1.0000

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle (C) 0 mg P-Trend	Low (L) 1 mg LP-LvsC	Mid (M) 3 mg P-MvsC	Mid-High (MH) 10 mg P-MHvsC	High (H) 30 mg P-HvsC	Saline (S) P-SvsC
Haemolympho-Reticular System	M-Granulocytic Leukaemia	1/60 (50) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000
	M-Histiocytic Sarcoma	0/60 (50) NC	0/60 (50) NC	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	1/60 (53) 0.5146
	M-Lymphocytic Leukaemia	1/60 (50) 0.6400	0/60 (50) 1.0000	0/60 (49) 1.0000	1/60 (49) 0.7475	0/60 (50) 1.0000	1/60 (53) 0.7668
	M-Malignant Lymphoma-Lympho (17)	1/60 (50) 0.5754	2/60 (51) 0.5075	0/60 (49) 1.0000	0/60 (49) 1.0000	1/60 (50) NC	0/60 (53) 1.0000
	M-Malignant Lymphoma-Lympho (253)	3/60 (50) 0.5231	2/60 (51) 0.8250	2/60 (49) 0.8126	6/60 (50) 0.2435	2/60 (50) 0.8189	1/60 (53) 0.9479
	M-Malignant Lymphoma-Lympho/ M-Malignant Lymphoma-	4/60 (50) 0.5514	4/60 (53) 0.6746	2/60 (49) 0.8932	6/60 (50) 0.3703	3/60 (51) 0.7900	1/60 (53) 0.9758
	M-Malignant Lymphoma-Plasma	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
	M-Malignant Lymphoma-Plasma/ M-Malignant Lymphoma-	3/60 (50) 0.8361	4/60 (50) 0.5000	4/60 (49) 0.4886	0/60 (49) 1.0000	2/60 (50) 0.8189	3/60 (53) 0.6884
	M-Malignant Lymphoma-Pleomo	3/60 (50) 0.8009	4/60 (50) 0.5000	3/60 (49) 0.6515	0/60 (49) 1.0000	2/60 (50) 0.8189	3/60 (53) 0.6884
Harderian Gland	B-Adenoma	7/57 (50) 0.9447	10/55 (49) 0.2817	3/54 (45) 0.9352	6/55 (48) 0.6962	3/58 (49) 0.9509	7/59 (52) 0.6430
Ileum	M-Adenocarcinoma	0/59 (49) NC	0/59 (49) NC	0/58 (48) NC	0/60 (49) NC	0/60 (50) NC	1/59 (52) 0.5149
Kidney	B-Adenoma	1/60 (50) 0.2304	1/60 (50) NC	1/60 (49) 0.7475	0/60 (49) 1.0000	2/60 (50) 0.5000	1/60 (53) 0.7668
	B-Adenoma/ M-Carcinoma	1/60 (50) 0.3006	1/60 (50) NC	2/60 (49) 0.4923	0/60 (49) 1.0000	2/60 (50) 0.5000	1/60 (53) 0.7668
	M-Carcinoma	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle (C) 0 mg P-Trend	Low (L) 1 mg LP-LvsC	Mid (M) 3 mg P-MvsC	Mid-High (MH) 10 mg P-MHvsC	High (H) 30 mg P-HvsC	Saline (S) P-SvsC
Liver	B-Haemangioma	0/60 (50) NC	0/60 (50) NC	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	1/60 (53) 0.5146
	M-Haemangiosarcoma	2/60 (50) 0.9629	1/60 (50) 0.8788	2/60 (50) NC	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000
	B-Haemangioma/ M-Haemangiosarcoma	2/60 (50) 0.9629	1/60 (50) 0.8788	2/60 (50) NC	0/60 (49) 1.0000	0/60 (50) 1.0000	1/60 (53) 0.8892
	B-Hepatocellular Adenoma	6/60 (50) 0.9203	6/60 (50) NC	9/60 (49) 0.2737	8/60 (49) 0.3713	3/60 (51) 0.9247	6/60 (53) 0.6607
	M-Hepatocellular Carcinoma	0/60 (50) 0.4041	1/60 (50) 0.5000	2/60 (49) 0.2424	4/60 (49) 0.0563	1/60 (50) 0.5000	2/60 (53) 0.2623
	B-Hepatocellular Adenoma/ M-Hepatocellular Carcinoma	6/60 (50) 0.8806	7/60 (50) 0.5000	11/60 (49) 0.1330	12/60 (49) 0.0880	4/60 (51) 0.8489	8/60 (53) 0.4335
Lung	B-Bronchiolo-Alveolar Adeno	10/60 (50) 0.7913	11/60 (50) 0.5000	14/60 (50) 0.2415	8/60 (49) 0.7682	9/60 (51) 0.7110	6/60 (53) 0.9321
	M-Bronchiolo-Alveolar Carci	6/60 (50) 0.3405	2/60 (50) 0.9703	4/60 (50) 0.8411	7/60 (50) 0.5000	5/60 (51) 0.7490	5/60 (53) 0.7701
	B-Bronchiolo-Alveolar Adeno/ M-Bronchiolo-Alveolar	16/61 (52) 0.6578	13/60 (51) 0.7922	18/61 (52) 0.4173	15/60 (51) 0.6422	14/60 (52) 0.7417	11/60 (54) 0.9269
Lymph Node, Mesenteric	B-Haemangioma	0/59 (49) 0.2830	1/57 (48) 0.4948	0/56 (46) NC	0/60 (49) NC	1/58 (49) 0.5000	0/56 (50) NC
Mandibular Salivary Gland	M-Sarcoma Nos	0/60 (50) 0.3992	0/60 (50) NC	0/60 (49) NC	1/60 (49) 0.4949	0/60 (50) NC	0/60 (53) NC
Pancreas	B-Islet Cell Adenoma	0/60 (50) 0.2016	0/60 (50) NC	0/60 (49) NC	0/60 (49) NC	1/60 (50) 0.5000	0/60 (53) NC
	M-Acinar Cell Adenocarcinoma	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
Penis	B-Squamous Cell Papilloma	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
Pituitary	B-Adenoma	0/60 (50) 0.5181	0/59 (49) NC	1/59 (50) 0.5000	2/59 (48) 0.2373	0/58 (49) NC	3/59 (52) 0.1287
	B-Adenoma/ M-Carcinoma	1/60 (50) 0.8170	2/59 (50) 0.5000	1/59 (50) NC	3/59 (48) 0.2933	0/58 (49) 1.0000	5/59 (53) 0.1164
	M-Carcinoma	1/60 (50) 0.8429	2/59 (50) 0.5000	0/59 (49) 1.0000	1/59 (48) 0.7423	0/58 (49) 1.0000	2/59 (53) 0.5221

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4A: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Male Mice (Continued)

Organ name	Tumor name	Vehicle (C) 0 mg P-Trend	Low (L) 1 mg LP-LvsC	Mid (M) 3 mg P-MvsC	Mid-High (MH) 10 mg P-MHvsC	High (H) 30 mg P-HvsC	Saline (S) P-SvsC
Seminal Vesicle	B-Adenoma	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
Skin/Subcutis	B-Benign Mast Cell Tumour	0/60 (50) 0.7984	1/60 (50) 0.5000	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
	B-Sebaceous Cell Adenoma	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
	M-Haemangiosarcoma	0/60 (50) 0.4800	0/60 (50) NC	1/60 (49) 0.4949	1/60 (49) 0.4949	0/60 (50) NC	1/60 (53) 0.5146
Sternum + Marrow	M-Haemangiosarcoma	0/60 (50) NC	0/60 (50) NC	0/60 (49) NC	0/60 (49) NC	0/60 (50) NC	1/60 (53) 0.5146
Stomach	M-Squamous Cell Carcinoma	1/60 (50) 1.0000	0/60 (50) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (50) 1.0000	0/60 (53) 1.0000
Tail	B-Schwannoma, Benign	1/58 (48) 1.0000	0/59 (49) 1.0000	0/56 (45) 1.0000	0/59 (48) 1.0000	0/57 (47) 1.0000	0/59 (52) 1.0000
	M-Osteosarcoma	0/58 (48) 0.5907	0/59 (49) NC	1/56 (45) 0.4839	0/59 (48) NC	0/57 (47) NC	0/59 (52) NC
Testis	B-Leydig Cell Adenoma	2/60 (50) 0.0007	1/60 (50) 0.8788	3/60 (49) 0.4903	0/60 (49) 1.0000	9/60 (50) 0.0256	1/60 (53) 0.8892
Thyroid	B-Follicular Cell Adenoma	0/60 (50) 0.6758	0/59 (50) NC	2/60 (49) 0.2424	0/60 (49) NC	0/59 (49) NC	0/59 (52) NC
Urinary Bladder	B-Mesenchymal Proliferative	0/60 (50) 0.5968	0/60 (50) NC	1/60 (49) 0.4949	0/60 (49) NC	0/60 (50) NC	0/60 (53) NC
Whole Body	B-Haemangioma	0/60 (50) 0.2787	1/59 (49) 0.4949	0/59 (49) NC	0/59 (48) NC	1/58 (49) 0.4949	1/59 (52) 0.5098
	M-Haemangiosarcoma	2/60 (50) 0.9426	2/59 (49) 0.6837	2/59 (50) NC	1/59 (48) 0.8711	0/58 (49) 1.0000	2/59 (53) 0.7130
	B-Haemangioma/ M-Haemangiosarcoma	2/60 (50) 0.8132	3/59 (49) 0.4903	2/59 (50) NC	1/59 (48) 0.8711	1/58 (49) 0.8750	3/59 (53) 0.5278

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.75 mg P - VC vs. L	Mid (M) 2.5 mg P - VC vs. M	High (H) 7.5 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Adrenal	B-Benign Phaeochromocytoma	0/60 (43)	0/60 (49)	0/60 (47)	1/60 (42)	0/60 (43)
		0.2320	NC	NC	0.4941	NC
	B-Subcapsular Cell Adenoma,*	0/60 (43)	1/60 (49)	0/60 (47)	0/60 (42)	0/60 (43)
		0.7624	0.5326	NC	NC	NC
Brain	B-Hemangioma	0/60 (43)	0/59 (48)	1/60 (48)	0/60 (42)	0/59 (43)
		0.4972	NC	0.5275	NC	NC
	M-Malignant Meningioma	0/60 (43)	0/59 (48)	0/60 (47)	1/60 (42)	0/59 (43)
		0.2333	NC	NC	0.4941	NC
	M-Malignant Oligodendroglio*	0/60 (43)	0/59 (48)	1/60 (47)	0/60 (42)	0/59 (43)
		0.4944	NC	0.5222	NC	NC
Connective Tissue	M-Liposarcoma	0/60 (43)	0/60 (49)	1/60 (47)	0/60 (42)	0/60 (43)
		0.4917	NC	0.5222	NC	NC
Femur + Marrow	M-Haemangiosarcoma	0/60 (43)	0/60 (49)	0/60 (47)	1/60 (43)	0/60 (43)
		0.2363	NC	NC	0.5000	NC
Haemolympho-Reticular System	M-Granulocytic Leukaemia	0/60 (43)	0/60 (49)	0/60 (47)	1/60 (42)	0/60 (43)
		0.2320	NC	NC	0.4941	NC
	M-Histiocytic Sarcoma	2/60 (43)	2/60 (49)	0/60 (47)	3/60 (43)	1/60 (44)
		0.2332	0.7394	1.0000	0.5000	0.8836
	M-Lymphocytic Leukaemia	0/60 (43)	2/60 (49)	2/60 (48)	3/60 (43)	0/60 (43)
		0.0856	0.2809	0.2755	0.1206	NC
	M-Malignant Lymphoma Nos	0/60 (43)	0/60 (49)	1/60 (48)	0/60 (42)	0/60 (43)
		0.4945	NC	0.5275	NC	NC
	M-Malignant Lymphoma-Lympho (17)	0/60 (43)	1/60 (50)	1/60 (48)	0/60 (42)	0/60 (43)
		0.6192	0.5376	0.5275	NC	NC
	M-Malignant Lymphoma-Lympho (253)	2/60 (43)	4/60 (49)	5/60 (48)	2/60 (42)	2/60 (44)
		0.6246	0.4029	0.2653	0.6831	0.7006
	M-Malignant Lymphoma-Lympho	2/60 (43)	5/60 (50)	6/60 (48)	2/60 (42)	2/60 (44)
		0.6800	0.2846	0.1721	0.6831	0.7006
	M-Malignant Lymphoma-Pleomo	5/60 (44)	2/60 (50)	10/60 (48)	4/60 (43)	5/60 (44)
		0.4235	0.9618	0.1724	0.7465	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.75 mg P - VC vs. L	Mid (M) 2.5 mg P - VC vs. M	High (H) 7.5 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Harderian Gland	B-Adenoma	3/54 (39)	3/56 (47)	2/58 (46)	3/59 (42)	3/50 (37)
		0.4861	0.7464	0.8671	0.6972	0.6371
	B-Adenoma/M-Adenocarcinoma	3/54 (39)	4/56 (47)	2/58 (46)	3/59 (42)	3/50 (37)
		0.5640	0.6046	0.8671	0.6972	0.6371
	M-Adenocarcinoma	0/54 (39)	1/56 (47)	0/58 (46)	0/59 (42)	0/50 (37)
		0.7759	0.5465	NC	NC	NC
Liver	B-Haemangioma	0/60 (43)	1/60 (49)	0/60 (47)	0/60 (42)	0/60 (43)
		0.7624	0.5326	NC	NC	NC
	M-Haemangiosarcoma	2/60 (44)	0/60 (49)	0/60 (47)	1/60 (43)	0/60 (43)
		0.5707	1.0000	1.0000	0.8751	1.0000
	B-Haemangioma/ M-Haemangiosarcoma	2/60 (44)	1/60 (49)	0/60 (47)	1/60 (43)	0/60 (43)
		0.6699	0.8979	1.0000	0.8751	1.0000
	B-Hepatocellular Adenoma	1/60 (43)	2/60 (49)	0/60 (47)	1/60 (42)	2/60 (43)
		0.6049	0.5494	1.0000	0.7471	0.5000
Lung	B-Bronchiolo-Alveolar Adeno*	2/60 (43)	5/60 (50)	8/60 (48)	2/60 (42)	5/60 (43)
		0.6755	0.2846	0.0653	0.6831	0.2166
	M-Bronchiolo-Alveolar Carci*	2/60 (43)	2/60 (50)	1/60 (47)	4/60 (44)	3/60 (44)
		0.1281	0.7464	0.8950	0.3492	0.5110
	B-Bronchiolo-Alveolar Adeno*/ M-Bronchiolo-Alveolar Carci*	4/60 (44)	7/60 (50)	9/60 (48)	6/60 (44)	8/60 (44)
		0.3679	0.3408	0.1518	0.3694	0.1760
Mammary Gland	M-Adenocarcinoma	3/56 (42)	1/55 (45)	4/58 (46)	1/55 (39)	3/59 (44)
		0.7087	0.9497	0.5514	0.9327	0.6840

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.75 mg P - VC vs. L	Mid (M) 2.5 mg P - VC vs. M	High (H) 7.5 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Ovary	B-Benign Luteoma	2/59 (42)	3/60 (49)	5/58 (45)	3/60 (42)	3/59 (43)
		0.3706	0.5735	0.2463	0.5000	0.5113
	B-Benign Mixed Sex Cord Str*	2/59 (42)	2/60 (49)	0/58 (45)	1/60 (42)	0/59 (43)
		0.7464	0.7476	1.0000	0.8795	1.0000
	B-Benign Sertoli Cell Tumour	3/59 (43)	0/60 (49)	0/58 (45)	0/60 (42)	0/59 (43)
		1.0000	1.0000	1.0000	1.0000	1.0000
	B-Benign Thecoma	0/59 (42)	0/60 (49)	0/58 (45)	0/60 (42)	1/59 (43)
		NC	NC	NC	NC	0.5059
	B-Cystadenoma	0/59 (42)	1/60 (49)	0/58 (45)	0/60 (42)	1/59 (43)
		0.7640	0.5385	NC	NC	0.5059
	M-Cystadenocarcinoma	1/59 (43)	0/60 (49)	0/58 (45)	0/60 (42)	0/59 (43)
		1.0000	1.0000	1.0000	1.0000	1.0000
	B-Haemangioma	0/59 (42)	0/60 (49)	0/58 (45)	0/60 (42)	1/59 (43)
		NC	NC	NC	NC	0.5059
	M-Leiomyosarcoma	0/59 (42)	1/60 (49)	0/58 (45)	0/60 (42)	0/59 (43)
		0.7640	0.5385	NC	NC	NC
	M-Tubulostromal Carcinoma	0/59 (42)	1/60 (49)	0/58 (45)	0/60 (42)	0/59 (43)
		0.7640	0.5385	NC	NC	NC
Pancreas	B-Islet Cell Adenoma	0/60 (43)	0/60 (49)	1/59 (47)	0/60 (42)	0/60 (43)
		0.4917	NC	0.5222	NC	NC
Pituitary	B-Adenoma	1/59 (42)	3/59 (48)	1/59 (47)	3/60 (42)	3/59 (44)
		0.2247	0.3604	0.7801	0.3079	0.3259
	M-Carcinoma	1/59 (42)	2/59 (49)	1/59 (47)	0/60 (42)	2/59 (43)
		0.8772	0.5582	0.7801	1.0000	0.5089
	B-Adenoma/M-Carcinoma	2/59 (43)	5/59 (49)	2/59 (47)	3/60 (42)	5/59 (45)
		0.4899	0.2750	0.7247	0.4887	0.2361

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.75 mg P - VC vs. L	Mid (M) 2.5 mg P - VC vs. M	High (H) 7.5 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Skin/Subcutis	B-Benign Hair Follicle Tumo*	0/60 (43)	0/60 (49)	1/60 (47)	0/60 (42)	0/60 (43)
		0.4917	NC	0.5222	NC	NC
	B-Squamous Cell Papilloma	0/60 (43)	2/60 (49)	0/60 (47)	0/60 (42)	0/60 (43)
		0.8152	0.2809	NC	NC	NC
	M-Fibrosarcoma	0/60 (43)	1/60 (49)	0/60 (47)	0/60 (42)	0/60 (43)
		0.7624	0.5326	NC	NC	NC
	M-Liposarcoma	0/60 (43)	0/60 (49)	0/60 (47)	1/60 (42)	0/60 (43)
		0.2320	NC	NC	0.4941	NC
	M-Mesenchymoma, Malignant	0/60 (43)	0/60 (49)	0/60 (47)	0/60 (42)	1/60 (44)
		NC	NC	NC	NC	0.5057
	M-Sarcoma Nos	0/60 (43)	2/60 (50)	0/60 (47)	1/60 (43)	0/60 (43)
		0.4239	0.2863	NC	0.5000	NC
Spleen	B-Haemangioma	0/60 (43)	0/60 (49)	1/60 (47)	0/60 (42)	0/60 (43)
		0.4917	NC	0.5222	NC	NC
Stomach	B-Adenoma	0/60 (43)	0/60 (49)	0/60 (47)	0/60 (42)	1/60 (43)
		NC	NC	NC	NC	0.5000
	B-Squamous Cell Papilloma	0/60 (43)	0/60 (49)	0/60 (47)	2/60 (43)	1/60 (43)
		0.0548	NC	NC	0.2471	0.5000
Thymus	B-Benign Thymoma	0/58 (42)	0/59 (49)	0/58 (46)	1/56 (41)	0/58 (43)
		0.2303	NC	NC	0.4940	NC
	M-Malignant Thymoma	1/58 (42)	0/59 (49)	0/58 (46)	0/56 (41)	0/58 (43)
		1.0000	1.0000	1.0000	1.0000	1.0000
	B-Benign Thymoma/ M-Malignant Thymoma	1/58 (42)	0/59 (49)	0/58 (46)	1/56 (41)	0/58 (43)
		0.4086	1.0000	1.0000	0.7470	1.0000
Thyroid	B-Follicular Cell Adenoma	0/59 (42)	0/60 (49)	0/60 (47)	1/60 (42)	0/60 (43)
		0.2333	NC	NC	0.5000	NC

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Table 4B: Tumor Rates and P-Values for Trend and Pairwise Comparisons in Female Mice (Continued)

Organ name	Tumor name	Vehicle (VC) 0 mg P - Trend	Low (L) 0.75 mg P - VC vs. L	Mid (M) 2.5 mg P - VC vs. M	High (H) 7.5 mg P - VC vs. H	Saline (SC) 0 mg P - VC vs. SC
Uterus	B-Adenoma	0/60 (43)	2/60 (49)	0/60 (47)	0/60 (42)	0/60 (43)
		0.8152	0.2809	NC	NC	NC
	B-Haemangioma	0/60 (43)	3/60 (49)	0/60 (47)	0/60 (42)	0/60 (43)
		0.8898	0.1467	NC	NC	NC
	M-Haemangiosarcoma	1/60 (43)	1/60 (50)	0/60 (47)	0/60 (42)	1/60 (43)
		0.9452	0.7889	1.0000	1.0000	NC
	B-Haemangioma/ M-Haemangiosarcoma	1/60 (43)	4/60 (50)	0/60 (47)	0/60 (42)	1/60 (43)
		0.9709	0.2313	1.0000	1.0000	NC
	B-Leiomyoma	3/60 (43)	1/60 (49)	2/60 (47)	4/60 (43)	2/60 (43)
		0.1519	0.9558	0.8461	0.5000	0.8200
	M-Leiomyosarcoma	1/60 (43)	0/60 (49)	1/60 (48)	0/60 (42)	2/60 (43)
		0.7459	1.0000	0.7795	1.0000	0.5000
	B-Leiomyoma/ M-Leiomyosarcoma	4/60 (43)	1/60 (49)	3/60 (48)	4/60 (43)	4/60 (43)
		0.2379	0.9804	0.8257	NC	NC
	B-Polyp, Endometrial Stromal	3/60 (43)	9/60 (51)	3/60 (47)	4/60 (42)	9/60 (44)
		0.6460	0.1074	0.7033	0.4866	0.0639
	M-Sarcoma, Endometrial Stro*	0/60 (43)	3/60 (50)	0/60 (47)	0/60 (42)	1/60 (43)
		0.8885	0.1510	NC	NC	0.5000
	M-Sarcoma, Endometrial Stro*/B-Polyp, Endometrial	3/60 (43)	12/60 (51)	3/60 (47)	4/60 (42)	10/60 (44)
		0.7851	0.0263	0.7033	0.4866	0.0376
	B-Polyp, Glandular	0/60 (43)	1/60 (50)	1/60 (47)	1/60 (42)	4/60 (44)
		0.2794	0.5376	0.5222	0.4941	0.0610
	M-Osteosarcoma	0/60 (43)	0/60 (49)	0/60 (47)	0/60 (42)	1/60 (43)
		NC	NC	NC	NC	0.5000
Vagina	M-Osteosarcoma	1/60 (44)	0/59 (49)	0/60 (47)	0/58 (40)	0/60 (43)
		1.0000	1.0000	1.0000	1.0000	1.0000
Whole body	B-Haemangioma	4/60 (39)	2/60 (47)	3/60 (45)	4/60 (39)	4/60 (39)
		0.3097	0.9253	0.8257	NC	NC
	M-Haemangiosarcoma	4/60 (39)	2/60 (47)	3/60 (45)	4/60 (39)	4/60 (39)
		0.3097	0.9253	0.8257	NC	NC
	B-Haemangioma/ M-Haemangiosarcoma	3/60 (41)	5/60 (45)	1/60 (46)	2/60 (41)	2/60 (41)
		0.7875	0.4314	0.9492	0.8126	0.8126

& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed;
NC = Not calculable.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

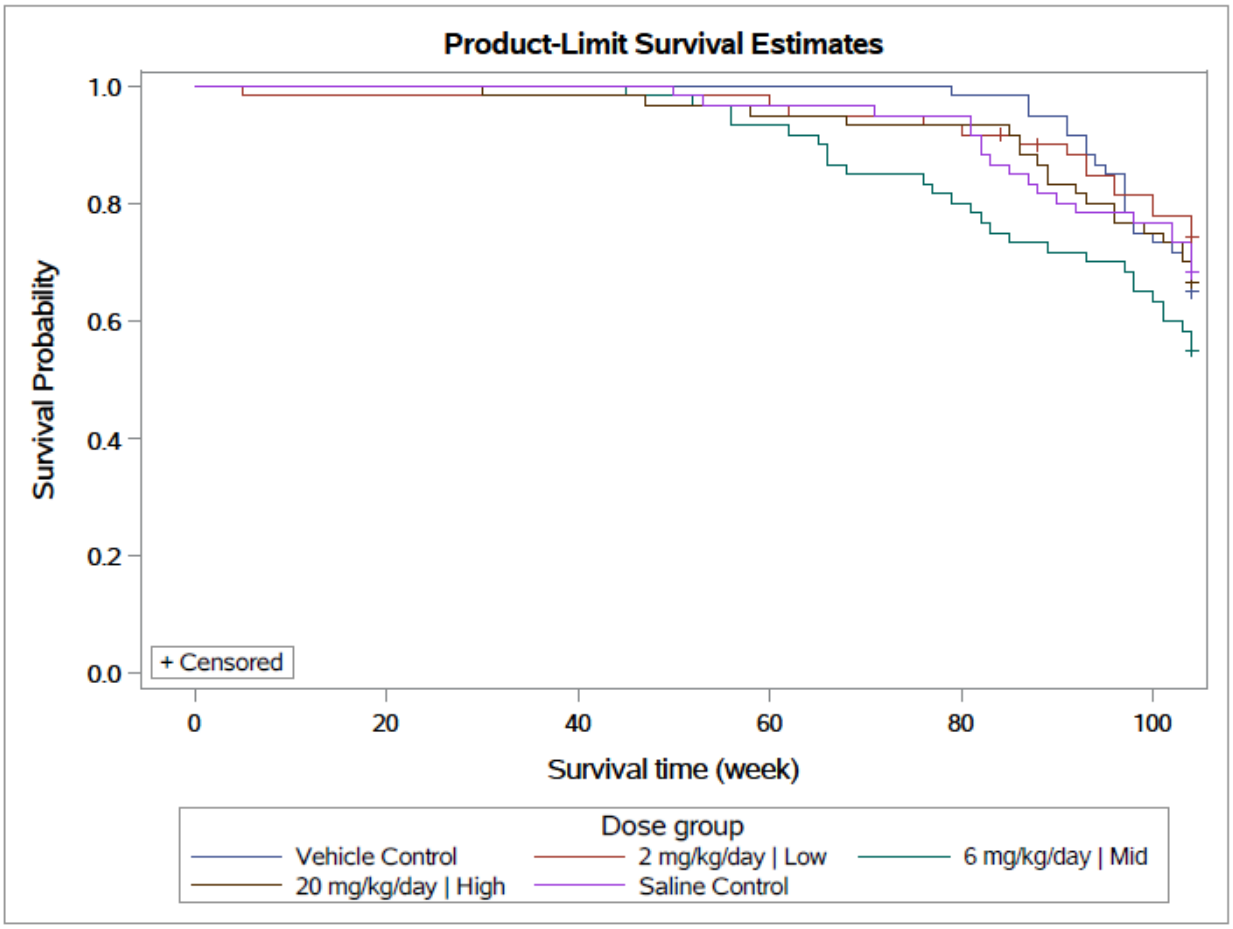


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

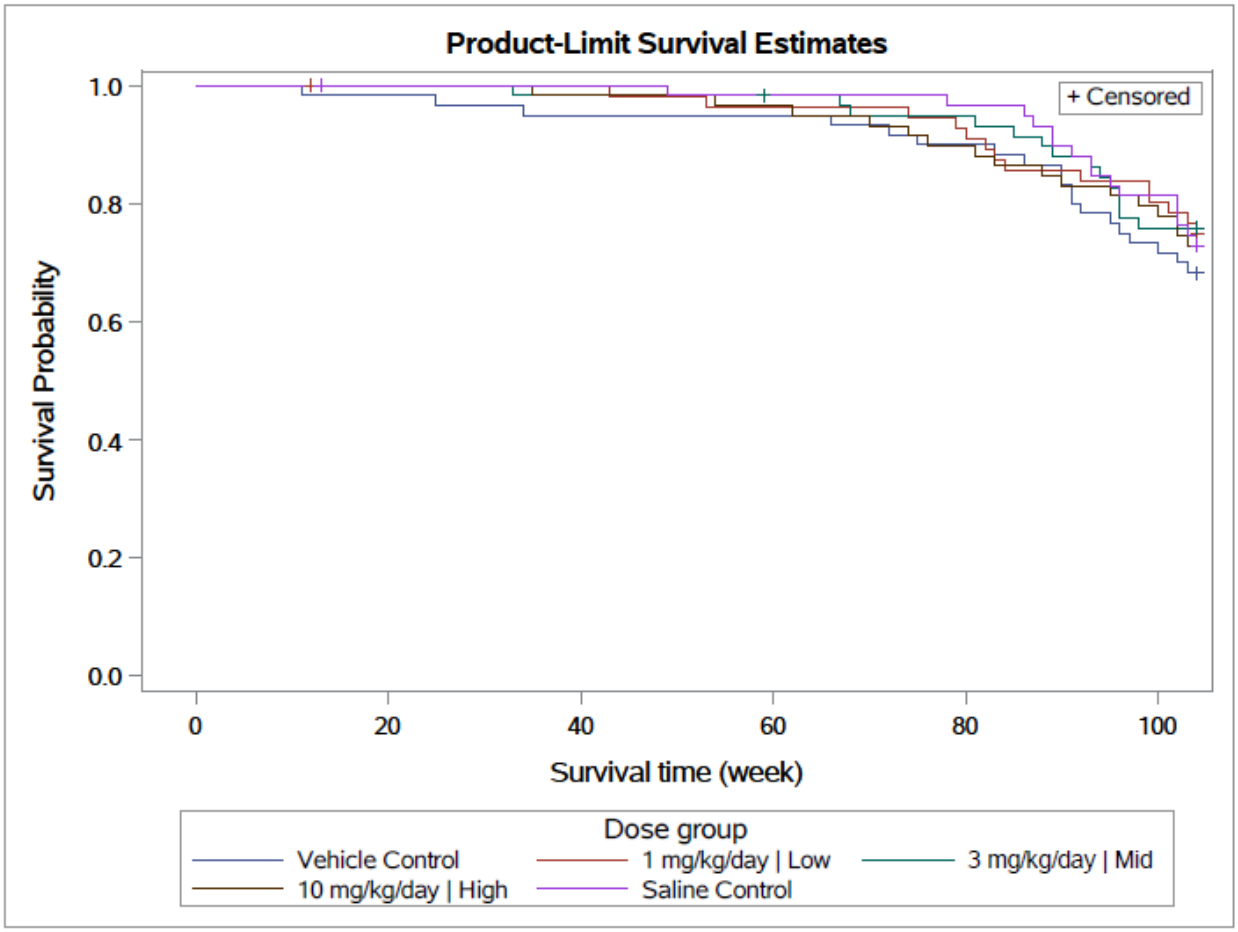


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

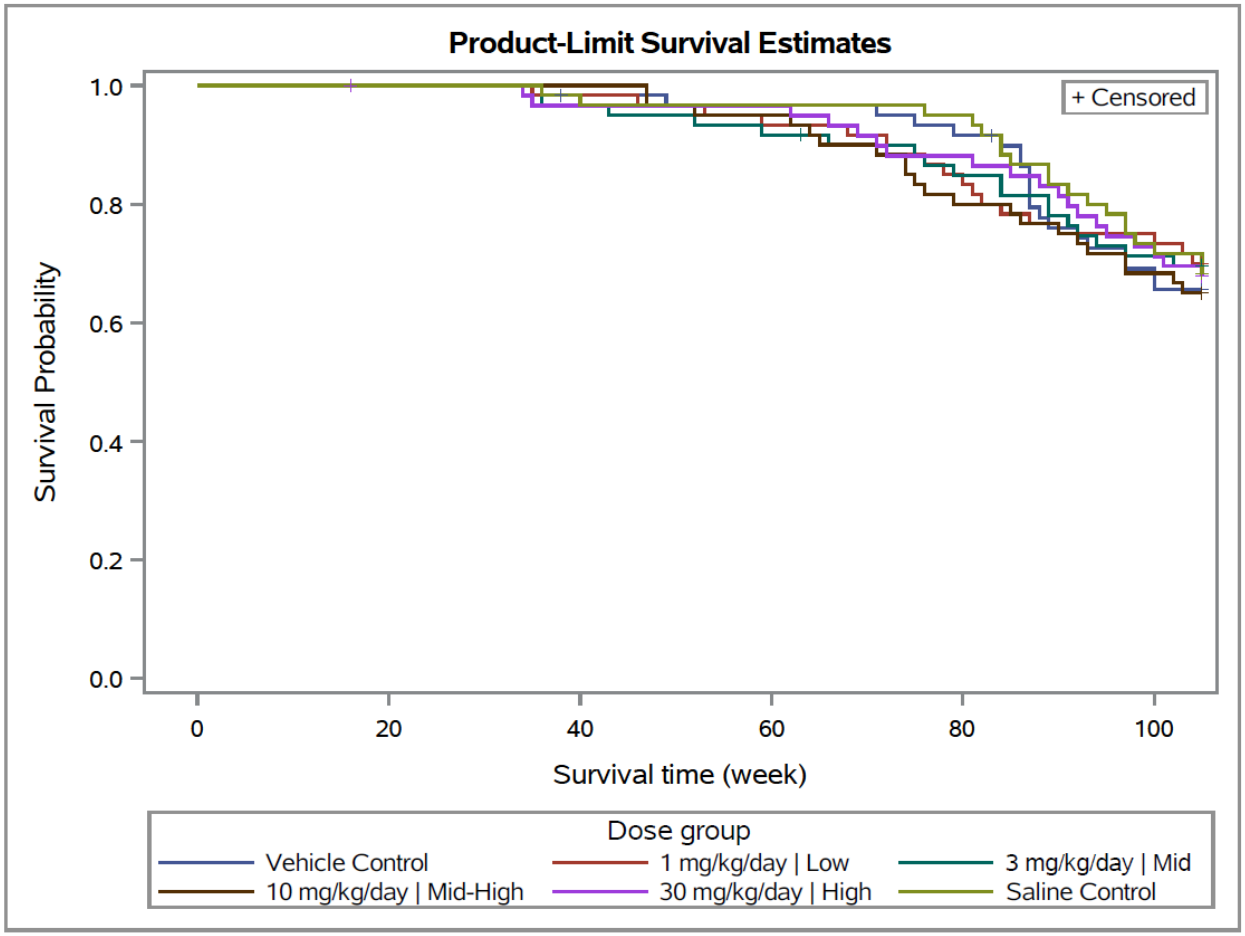
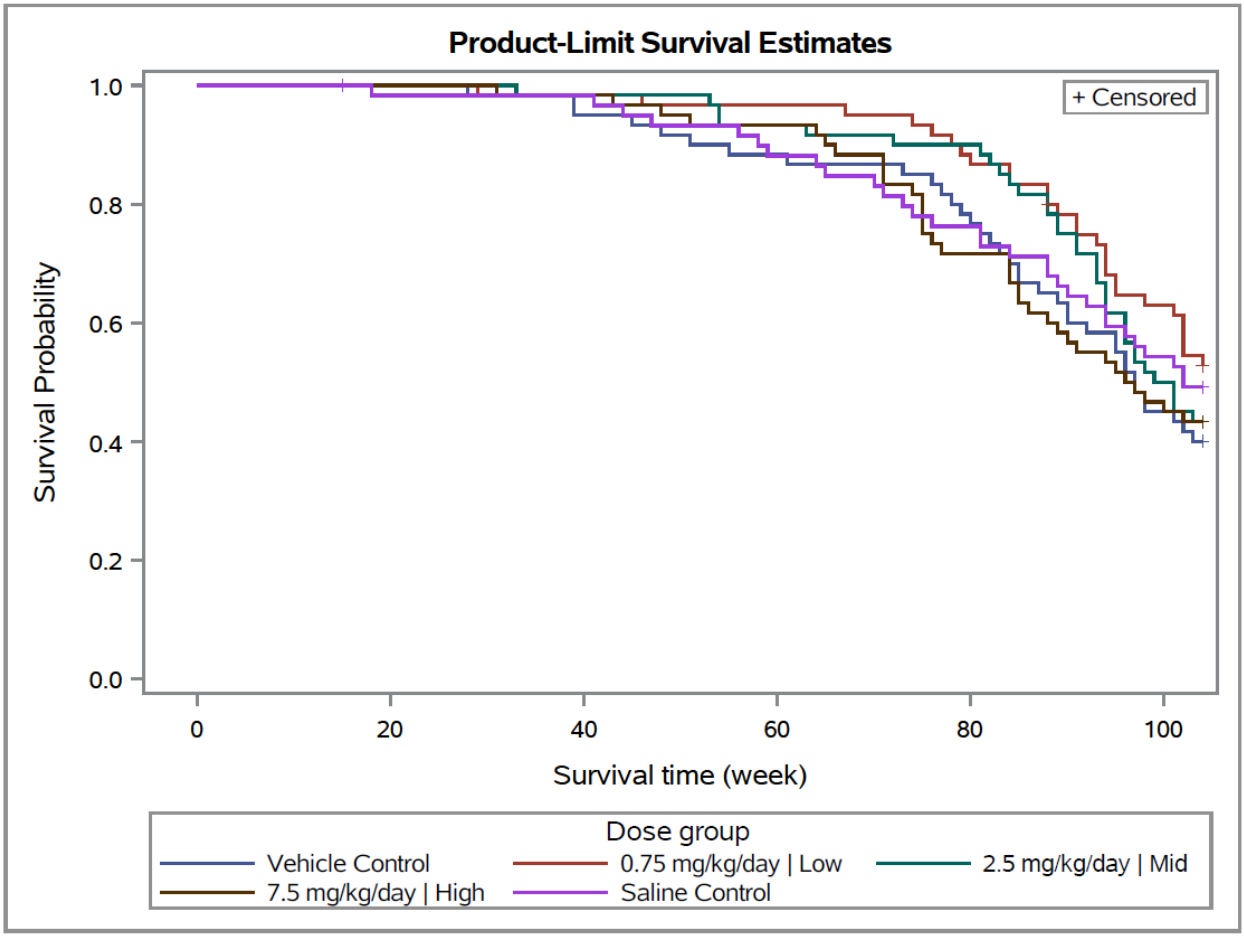


Figure 2B: Kaplan-Meier Survival Functions for Female Mice

6.



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Concur with review.